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# LATE NONTUBERCULOUS COMPLICATIONS OF CALCIFIED HILUS LYMPH NODES<sup>1 2</sup>

JEROME R. HEAD AND CHESTER W. MOEN

(Received for publication June 16, 1948)

## INTRODUCTION

In most instances, primary tuberculosis of the lungs is a benign infection. The focus in the lung and the larger centers in the hilus and mediastinal lymph nodes pass through their acute stages without producing important symptoms or complications, and usually the permanent calcifications which result are matters of pathological and roentgenological interest, rather than of clinical importance. This is not always the case. Guersant, Le Blond (1), and Laennec (2) reported numerous cases in which acutely inflamed tuberculous nodes had occluded and ruptured into the bronchi, lung, trachea, and esophagus, producing extensive and fatal disease. Parrot (3), Hutinee (4), and Kuss (5) noted this, and that the primary focus in the lung could progress to caseation and excavation and to the development of widespread tuberculous pneumonia. They observed also that the infection could pass beyond the nodes to involve the thoracic duct and produce milary tuberculosis. More recently, Kent (6) has pointed out that the entity commonly called epituberculous pneumonia is in reality an atelectasis caused by enlarged hilus lymph nodes, and Lightwood and Wilson (7), Hughes and Simpson (8), and Huizinga (9) have shown that a transient atelectasis so produced during the acute stages of primary tuberculosis is a common cause of chronic nontuberculous bronchiectasis.

These are all complications of the acute phases of the primary tuberculous complex. The subject of this paper is the late nontuberculous complications of healed or quiescent calcified tuberculous nodes at the root of the lung. As has already been stated, the acute primary infection in these nodes usually progresses to spontaneous arrest and to calcification. In most cases this is an encapsulation and an arrest and not a cure of the infection. Tubercle bacilli remain alive in the nodes for many years and extension from this source is a common cause of reinfection bronchial and parenchymal tuberculosis. That in itself is a large and important aspect of the pathogenesis of tuberculosis. It does not fall within the scope of this paper, however, which is concerned only with the late nontuberculous activation of these calcareous nodes. However long these calcifications may have been present, and in spite of the absence in them of live tubercle bacilli, they can, and frequently do, become secondarily infected and enlarge to press upon, occlude and perforate the bronchi and even the esophagus with the production of recurring pneumonia, atelectasis, bronchi-

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<sup>2</sup> Presented before the Medical Section, as part of the symposium on *Surgery-Trends-Late Results*, at the 44th Annual Meeting of the National Tuberculosis Association, New York, New York, June 16, 1948



ectasis, and lung abscess. Such activation is frequently associated with hemoptysis and, what is more dramatic, with the expectoration of particles of calcium. The condition can be the cause of nearly every type of pulmonary infection and frequently produces a clinical picture scarcely distinguishable from bronchial carcinoma. For these reasons, it has seemed worthwhile to recall attention to it and to emphasize that it is common and not rare, and that it can be present without being signaled by the expectoration of calcium.

#### HISTORY

Nontuberculous disease of the lungs associated with the expectoration of calcareous particles has been noted since the earliest times. Aristotle, in the course of dissections of animals carried out at the instigation of Alexander the Great, noted that the lungs frequently showed rock-like indurations similar to those found in the spleen and kidney (4). Aretaeus of Cappadocia and Galen reported cases of cough with expectoration of stones (4). Galen conjectured that they were formed in the bronchi by the drying of thick secretions. Alexander of Tralles reported the history of a man who expectorated calcareous concretions so large that they made a noise when they struck the ground. Paulus Aegineta saw the expectoration of many stony concretions associated with hemoptysis. Poulahon, who wrote a treatise on the subject in 1891 and who is the source of much of this historical review and bibliography, mentions similar cases reported by various ancient authors (4).

In 1600 Schenck (4) reviewed the subject and cited the case of Dr. Oswald Gabelhower who was cured of chronic lung disease by the expectoration of a calculus. He mentioned many similar cases reported by various physicians.

In 1720, Richard Morton (10) in his classification of types of phthisis included that produced by calculi. He wrote

I have often observed chalky stones bred in the lungs, which, when they have been angular and disturbed with the shaking of the lungs, are wont to tear the tender substance of those parts, from whence have arisen a violent and dry cough and a horrible pain in the breast, like that in Pleurisy and Peripneumony, sometimes also in hemoptysis with a considerable flux of blood and from thence ulcers, with the usual signs of a consumption of the lungs. Therefore, when these horrid pains happen with an hemoptysis about the beginning of a consumption, we may justly suspect it to be a consumption from stones in the lungs, although we cannot pronounce anything certain of this thing until the stones have been coughed up. Usually these stones get into the windpipe by which they are coughed up, and that seldom without a great flux of blood. But if the stones are smooth they may occasion only a dry cough and something of an oppressing weight in the breast. But when angular, and sharp, they break and tear the lungs and cause pain, spitting of blood, ulcers, and a consumption itself, as I have hinted.

In 1746, Boerhaave (11) wrote

The celebrated botanist, Vullant, spit up 400 stones from his lungs before death, though they were all of them indeed small and round. He was afflicted with an asthma from a calcareous matter collected in the vesicles of the lungs. I have seen asthmatics of the worst kind, in which the patient has been tortured with incessant coughing without intermission, 'til after some weeks they have brought up calculi from the windpipe, and the respiration has been free for some time, 'til more calculi were again formed. I have seen other patients who have kept by them large cups full of these stones which had been brought up from the lungs. Such people as these die with a spitting of blood, for the tender fabric of the lungs is destroyed by the violent coughing used to bring up these stones.

In 1761, Moigagni (12) described the clinical and pathological findings in such cases. In a letter to William Bromfield of London he wrote in detail of the respiratory troubles resulting from the presence of concretions in the lungs. Poulahon states "He established the distinction between deposits in the lungs, in the bronchial glands and those formed within the bronchi from the condensation of secretions" (4).

It was not until the early nineteenth century that calcifications within the lung and bronchial nodes were recognized as being the result of tuberculosis. Bayle (13) considered calcareous phthisis as distinct from tuberculous phthisis. Broussais (4) and Laennec (2) were the first to insist on their tuberculous origin. This confusion arose undoubtedly from the fact that the expectoration of calcium was sometimes associated with active tuberculosis and sometimes with acute or chronic nontuberculous pulmonary infections.

In 1891, Poulahon (4) included in his thesis a section on what he termed "pseudo-tuberculeuse calculaire." At this early date he mentions the fact that actinomycosis, chidothricosis, and other mycotic infections can produce pulmonary calcifications.

Since that time, as before, there have appeared numerous reports of individual cases or of groups of cases. These appear in articles by Bickel and Grunmach (14), Pritchard (15), Pendergiass (16), Pratten (17), Stivelman (18), Lloyd (19), Van Ordstrand (20), Anderson and Mackey (21), Arthur Elliott (22), Myers (23), Tinney and Moersch (24) and Maytum and Vinson (25). Most of these are reports of one or of a few cases. Van Ordstrand (20) described thirteen cases observed between 1900 and 1930, and Tinney and Moersch (24) twenty-eight cases collected from the files of the Mayo Clinic.

#### ETIOLOGY

Just why a healed and encapsulated calcified node, after remaining stationary and innocuous for many years, should suddenly begin to cause trouble is uncertain. In the cases under consideration, it is not a reactivation of a latent tuberculosis, for tubercle bacilli are not found and the resulting parenchymal infection is not tuberculous. One must conclude, I believe, that the calcium, like any other foreign body, invites secondary infection and that when such infection occurs it persists until the foreign body has been removed or extruded. Such late secondary infection develops about calcium deposits in the lung parenchyma and about layers of calcium deposited on the pleura.

There are four routes by which bacteria could reach calcified hilus lymph nodes (1) by direct extension from infection and ulceration of the bronchial wall, (2) by extension from contiguous lung tissue, (3) by way of the blood stream, and (4) by way of the lymphatics. Which is the usual route is a matter for speculation. It seems probable that the nodes, not being completely involved, continue to function as lymph nodes and that bacteria reach them by way of the lymphatics from infections of the lung parenchyma. It is certain that in many instances uninfected calcified nodes produce a permanent narrowing of a contiguous bronchus and that this narrowing predisposes to recurring infection in the distal bronchi and parenchyma. Such a node is more exposed to infection than one which does not drain a repeatedly reinfecting lobe.

#### ANATOMICAL OBSERVATIONS

The regularity in position of the hilar lymph nodes was pointed out by H. P. Nelson (26) in 1932. This consistency in the relation of the hilar nodes to the

bronchial tree and pulmonary vessels was also noted in our series of fifty cadaver dissection. From the case reported in the literature and in this paper, it is noted that the most frequent sites of stricture and perforation by enlarged nodes were in those portions of the bronchi where lymph nodes were normally found.

The important bronchial nodes present were as follows:

In the right hilum were three large nodes which were present in 100 per cent of the cases. The largest of these was seen from the posterior aspect of the hilum and was present in the angle of the bifurcation of the trachea, the greater part of the node lying in contact with the medial surface of the right main stem bronchus. Another large node was present between the under surface of the upper lobe bronchus and the main stem bronchus. It partially encircled the upper lobe bronchus in all cases. The third node was located in the angle formed by the middle and lower lobe bronchi. This was the smallest of the three nodes and averaged one cm. in diameter. Another node in the right hilum which is often regarded as important was located in the angle formed by the trachea and the right main stem bronchus. However, in our series, this node was present in only 20 per cent of the cases and averaged but 7.6 mm. in diameter.

In the left hilum there were also four principal bronchial nodes. Only one of these was present in 100 per cent of the cases. This node was located between the lingular bronchus and the lower lobe bronchus. From the anterior aspect in the angle formed by the left main stem bronchus and the left upper lobe bronchus was a large node which was present in 80 per cent of the cases. From the posterior aspect of the left hilum, a large node was seen on the upper border of the main stem bronchus in 80 per cent of the cases. Another large node was seen on the inferior surface of the main stem bronchus in 70 per cent of the cases. The last two nodes were present together in the same specimen in 44 per cent of the cases.

#### SITE OF PERFORATION

With the anatomic position of the bronchial nodes in mind, the opinions of various authors regarding the most frequent site of perforation will be given.

M. Pammz (27) stated that there was a prevalence of perforation on the right side on the medial wall of the right main bronchus, i.e. the interbifurcation node was the greatest offender.

B. Schick (28) mentioned that the right main bronchus was most frequently affected by stones because of the increased frequency of the primary complex on the right.

S. Engel (29) stated that the right bifurcation node and the right tracheal node were most frequently affected and that the majority of perforations occurred in this area.

C. Petot (30) demonstrated anatomically that the lymph nodes to be most frequently enlarged and to exert pressure were those found surrounding the right stem bronchus in the area of the bronchus to the right middle lobe.

In 1911 O. Auerbach (31) reported his examination of the bronchial tree in 1,656 autopsies in which he found 22 perforations. In his series he found that perforations occurred most frequently in the area of the carina, but that the

distribution was fairly equal between the trachea, the right and the left main stem bronchi

The cases reported in the literature reveal almost equal distribution of involvement among the bronchi to all the lobes, with the exception of the right upper lobe bronchus which was affected the most (30 per cent of all cases), and the lingular bronchus which was not affected at all

In our cases the frequency of involvement was distributed among the right upper, the left upper, and the middle lobe bronchi, respectively

#### CLINICAL PICTURE

The symptoms and physical and roentgenographic findings can simulate every type of acute and chronic bronchial and pulmonary disease. Basically, all of the findings are caused by bronchial ulceration, narrowing, and occlusion. Hemorrhage may be the only symptom. *There may be merely recurring attacks of bronchopneumonia in the same lobe.* The cough associated with this is apt to be severe and spasmodic. Blood streaking or frank hemorrhage are common. During the acute stage a persistent wheeze localized over the affected lobe is a common and suggestive sign. This may disappear after the expectoration of calcium. Lung abscess and empyema may complicate the lung infections.

Recurring attacks of acute atelectasis produce a dramatic picture. Poulahon (4) speaks of sudden attacks of bronchial colic associated with dyspnea, fever, and relieved by the expectoration of calcium. Morton comments on the "horrid pain" in such cases (10). The atelectasis may persist and all types of chronic pulmonary suppuration may develop.

Attacks tend to be recurrent. They usually stop finally and one can assume that this occurs when all of the calcium has been extruded, yet Boerhaave's patient expectorated 400 stones over a period of many years (11).

In one case in the present series, the calcified gland at the bifurcation ruptured into the right lower lobe bronchus and also into the esophagus, producing an esophageal bronchial fistula.

The most dramatic symptom is the expectoration of stones. These may vary in size from small and sand-like grains to particles one cm. in diameter. It is surprising how often the patient fails to be impressed with this finding sufficiently to report it to his physician. For this reason it is necessary to question all patients on this specific point. When so questioned, one of our patients produced from his wallet an envelope containing a dozen or more stones. He had never shown them or mentioned them to any of the many doctors who had attended him.

The roentgenographic findings are as variable as the bronchial and pulmonary conditions which are produced. One must suspect the condition and remember that calcifications at the root of a lobe may be responsible for disease in the parenchyma. Laminography may give important information in revealing a calcified node impinging upon a bronchus.

Bronchoscopy rarely shows more than granulation tissue and bronchial narrowing. Manipulation often produces important bleeding.

## TREATMENT

The treatment depends upon the nature, the severity, and the chronicity or recurrence of the symptoms. In many instances the calcium is extruded and expectorated spontaneously, the fistula in the bronchus closes without producing important narrowing, and the infection in the lung clears up. There may be only one such episode or they may recur at indefinite intervals.

In such cases, and in all cases at first, medicinal treatment of the parenchymal infection is all that is indicated. Lung abscess or empyema may develop and may require surgical treatment. In one case in this series an esophageal bronchial fistula produced a threatening situation. That it closed following endoscopic cauterization of the openings seems fortuitous. Such a complication today would be an indication for surgical intervention.

Bronchoscopic removal of the calcium is difficult and dangerous. The nodes and bronchi are contiguous to large pulmonary vessels. Bleeding is apt to be severe and may be fatal.

If the infection persists or recurs with bothersome frequency, lobectomy is indicated. If the offending node is not infected at the time of the operation and the bronchus is not greatly narrowed, removal of the node may be feasible and sufficient.

## CASE REPORTS

*Case 1* A male, age 38, was first admitted to the hospital on December 19, 1946, complaining of a nonproductive cough and wheeze for three weeks. There were flecks of blood in his sputum and on three occasions he had coughed up small solid particles "like chalk." On the day of his admission, he coughed up some more particles which relieved his cough considerably. Physical examination revealed no significant findings. His temperature was 99.4°F. The total erythrocyte count was 4.7 million per cu mm and the total leukocyte count was 9,650 per cu mm. Roentgenographic examination revealed no abnormalities except for calcified deposits in the right hilus. The bronchoscopic examination revealed a white mass arising from the posterior wall of the bronchus at the origin of the right upper lobe bronchus. This was interpreted as calcium. The manipulation of this mass by forceps produced a brisk hemorrhage and bronchoscopy was discontinued. The patient continued to wheeze and cough for another week and then suddenly developed a chill and fever of 103°, accompanied by a leukocytosis of 23,000 cells per cu mm. Physical examination revealed increased breath sounds and some scattered rales over the area of the right lower lobe. Roentgenographic examination revealed a light, hazy, bronchopneumonic type of infiltrate in the lower portion of the right lung. The following night (January 1, 1947) he had another chill and fever of 103°. At the same time he had a severe coughing attack and brought up a large calcified plaque (figure 1). Immediately after coughing up the calcium, the patient noted a disappearance of his wheeze. A daily remission of temperature followed and it was normal on January 7, 1947. The chest roentgenogram on this date was also normal.

*Case 2* (Figure 2) A man, age 34, began to have frequent colds and to cough up foul-smelling sputum and small flecks of blood in September 1944. At the same time he began to wheeze and cough up small pieces of stone from time to time. On November 19, 1944, he had a chill and fever of 103°F and was admitted to an Army hospital. He was coughing up a cupful of pus daily and was then given penicillin and sulfonamide therapy. He improved clinically but there was little change on the chest roentgenogram. Again in April 1945, he



FIG 1 (Case 1) Stones expectorated by this patient. The large mass was an amalgam of pieces of calcium and blood clot.

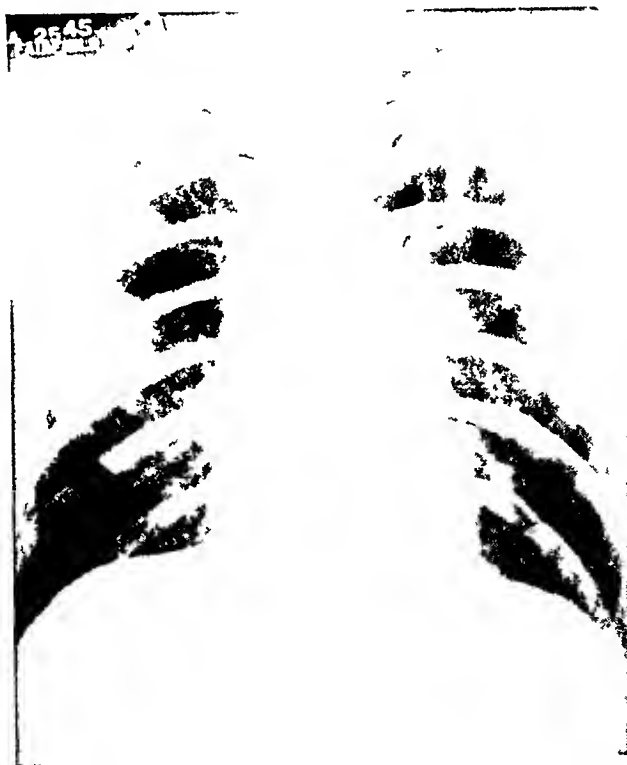


FIG 2 (Case 2) Small lung abscess peripheral to calcified lymph node. This patient coughed up approximately one-half ounce of small stones over the course of several months.

had another episode of chills and fever with expectoration of much foul pus. Another course of penicillin was given and again he improved clinically but without much change on the roentgenogram. On June 20, 1945, the patient came into the office with a jar containing a great number of stones he had coughed up a few days before. By the first week in July 1945, his chest roentgenogram was almost normal and his wheeze had diminished a great

deal, although he was yet coughing up small particles of calcium. Bronchoscopy at this time revealed a friable mass of tissue on the medial aspect of the right main bronchus at the level of the right middle lobe bronchial orifice. The lower lobe orifice was stenotic but smooth.

*Case 3* (Figure 3) A woman, age 43, was admitted to the hospital February 26, 1944, complaining of severe coughing attacks and wheezing for the past three days. She stated that she had had similar attacks on several occasions since 1941. Sometimes the attacks had been accompanied with chills and fever. On admission the total erythrocyte and leukocyte counts were normal. The chest roentgenogram appeared similar to the one taken in 1941,



FIG. 3 (Case 3) Area of pneumonia and abscess distal to eroding calcified nodes

which revealed a large primary complex in the hilus of the right lung with parenchymal infection about it. Bronchoscopy revealed granulation tissue and constriction at the beginning of the right main stem bronchus at the level of the carina. Two weeks later the patient coughed up several pieces of calcium which gave her considerable relief from cough and wheezing. Again during the first week in April 1944, she coughed up some more calcium. After this her roentgenogram showed considerable clearing.

*Case 4* (Figures 4A and B) A man, age 36, had empyema and pneumonia in 1933. In June 1943, he developed a cough, had pain in his left chest, dyspnea, and a fever of 102° F. The roentgenographic examination revealed several calcified nodes at the hilus of both lungs and an area of parenchymal infiltration radiating outward from the left hilus to the infracolicular area. Repeated sputum examinations, cultures, and guinea pig inoculations were negative for tubercle bacilli. However, the patient was advised to be on bed rest. He stayed in bed until October 1943 with little improvement symptomatically or on the chest

roentgenogram. In the first week of October, he had a severe coughing attack and brought up several large pieces of calcium. Roentgenographic examination on November 15 showed almost complete clearing of the lesion (figure 1B). Since then he has been completely well.



FIG. 1 (Case 1)

A (Left) Bronchopneumonia in left upper lobe peripheral to calcified gland eroding into the bronchus.

B (Right) After expectoration of stones.



FIG. 5 (Case 5) Infiltration in left upper lobe which cleared following expectoration of particles of calcium.

*Case 5* (Figure 5) Three weeks prior to admission, a 42 year old man began having daily episodes of hemoptysis, small in amount, not associated with any pain. He had no fever on admission and the total leukocyte count was normal. The chest roentgenogram revealed an increased density along the left side of the mediastinum just above the hilus. Within this area of density were several calcium deposits. Extending outward and upward from this area were some fibrous strands which brought up the question of an old tuberculous or malignant process. Bronchoscopy showed a bleeding area at the orifice of the upper lobe.



bronchus. Bronchial secretions were negative for tumor cells. One week after admission, the patient coughed up several pieces of calcium. Two days later the area of increased density had disappeared from the chest roentgenogram.

*Case 6* (Figure 6). A 49 year old white woman had a severe grinding pain behind the xiphoid process five weeks prior to admission. At the same time she developed a cough which was deep seated and paroxysmal. Two weeks later she had an identical attack and expectorated some pus and several small pieces of calcium. One hour prior to admission she had another coughing attack with substernal pain during which she had an hemoptysis which filled an emesis basin. After hospitalization the cough subsided considerably.



FIG 6 (Case 6). Broncho esophageal fistula secondary to erosion of calcified node into the bronchus and esophagus. After expectoration of calcium and cauterization of fistulous openings through the bronchoscope and esophagoscope, patient made a complete recovery.

Röntgenographic examination of the chest revealed no abnormalities. After ten days the patient began to have difficulty in swallowing and coughed severely after eating and drinking. Barium studies of the esophagus revealed a definite tracheo esophageal fistula approximately at the level of the bifurcation of the trachea (figure 6). Through the bronchoscope, a nipple like protrusion in the posterior wall of the right main bronchus immediately below the bifurcation was seen. Esophagoscopy revealed a fistula along the right lateral wall, 30 cm from the teeth. Gastrostomy was done. Two weeks later the patient developed a lung abscess which was drained satisfactorily. After three months the fistulous tract had healed and the gastrostomy tube was withdrawn. For the past four years the patient has been well.

*Case 7* (Figures 7 A and B). A woman, age 25, was admitted to the Veterans Hospital in May, 1947, complaining of a chronic, productive cough of two years' duration. The cough

had gradually become more severe and the sputum more purulent. On five separate occasions the patient had expectorated a teaspoonful of bright blood. The first hemoptysis occurred in October 1915, and the last in April 1947. In October 1945, the chest roentgenogram was negative, but a second examination in February 1946 revealed a "possible lung abscess in the right middle lobe." At this time the patient had no fever, but a course of penicillin and sulfanilamide was given. There was no improvement either clinically or on the chest roentgenogram. In November 1946, she expectorated a piece of calcium "one half inch in diameter" along with a tablespoonful of blood. During her recent admission the patient had no fever. The physical examination was essentially negative and tubercle bacilli were not found in the sputum. Roentgenographic examination revealed an atelectatic middle lobe and a large calcified node near the origin of the middle lobe bronchus (figures 7 A and B). Bronchoscopy revealed a stenotic middle lobe orifice. Examination of material obtained by biopsy of this area was negative for tumor tissue. After three months there was spontaneous clearing of the middle lobe atelectasis.



FIG 7 (Case 7)

A (Left) Atelectasis of the middle lobe caused by erosion of calcified node into the bronchus

B (Right) Oblique film on same patient

**Case 8 (Figures 8 A and B)** A 40 year old man was admitted to the Veterans Hospital August 5, 1947, complaining of a chronic, productive cough since October 1946. At that time he had been admitted to a hospital with acute symptoms of chills, fever, cough, and chest pains. A diagnosis of pneumonia was made and he had been treated with penicillin and sulfadiazine. His acute symptoms abated but the chronic, productive cough persisted. Because of this cough he came to the Veterans Hospital for treatment. The significant physical findings were confined to the right chest posteriorly. In this area there was increase in tactile fremitus, impairment of resonance, and depression of breath sounds. The chest roentgenogram revealed an area of increased density at the right base and numerous calcified glands in the region of the right hilus (figure 8 A). This was interpreted as atelectasis produced by the calcified nodes. Bronchoscopy revealed a narrowing of the right middle lobe bronchus, and a study of the bronchial secretions was negative for tumor cells. The bronchogram showed an abrupt obstruction of the right middle lobe bronchus with pooling of the lipiodol at this point (figure 8 B). Since the presence of carcinoma could not be excluded, thoracotomy was performed. The right middle lobe was completely atelec-



FIG 8 (Case 8)

A (Left) Atelectasis of the middle lobe caused by erosion of calcified node into the bronchus

B (Right) Lateral film of same patient after injection of iodized oil showing the occluded bronchus

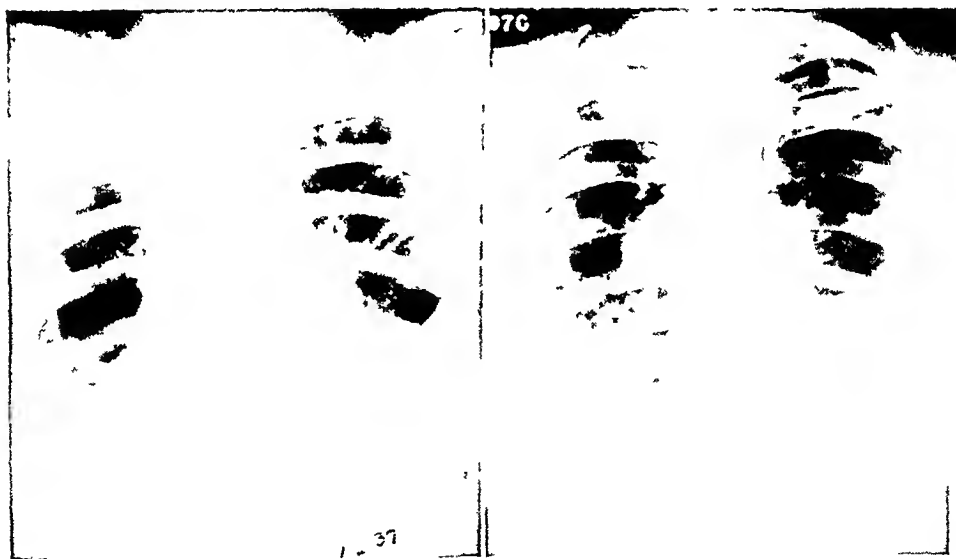


FIG 9 (Case 9)

A (Left) Atelectasis of right upper lobe caused by perforation of calcified nodes into the bronchus

B (Right) Roentgenogram of same patient after expectoration of numerous particles of calcium

tatic and many calcified nodes were adherent to the origin of the middle lobe bronchus. Lobectomy was performed with difficulty and microscopic examination of the bronchus revealed only granulation tissue. The postoperative course was uneventful.

*Case 9* (Figures 9 A and B) A woman, age 40, was first seen in a California clinic on June 1, 1937. She complained of chest pain of four months' duration, cough for one month, and weight loss of 20 pounds in six months. The physical examination was essentially negative. The roentgenographic examination revealed a tumor mass at the right superior mediastinum which appeared to be a node. In addition, there was an area of increased density involving the upper third of the right lung. Bronchoscopy revealed the presence of creamy pus exuding from a compressed right upper lobe bronchus. Examination of the smear revealed gram-positive cocci but no acid-fast organisms. The serologic test for syphilis was also negative. The patient was given fifteen courses of deep X-ray therapy and in September 1937 the dense area in the right upper lobe had decreased considerably so that numerous calcium deposits could be seen in the right hilus. The cough and pain subsided. The patient entered the Northwestern clinic in October 1937, complaining that her chest pain and cough had reappeared. Physical examination revealed rhonchi and wheezes over the right upper lobe. The chest roentgenogram was essentially the same as the last one taken. The patient was again treated with deep X-ray therapy and cough medicines. The cough persisted until December 1938, when she coughed up a matchbox full of stones. This relieved her cough for a few months and then it recurred. She coughed up stones again in 1940, 1943, and in May 1944. Her last visit to the clinic was in August 1944. At that time her cough was almost gone and bronchoscopy revealed a normal bronchial tree.

*Case 10* A man, age 51, was admitted to the Veterans Hospital complaining of chronic cough with the expectoration of blood and pus for the past year. On several occasions he had expectorated calcium plaques together with considerable quantities of blood. Roentgenographic examination revealed an increased density and numerous calcium deposits in the upper part of the left hilus. Bronchoscopy revealed a fixation of the left bronchus with some distortion and roughening of the lateral wall above the upper lobe orifice. Examination of the material obtained by biopsy of this area revealed tumor cells. One week after admission he coughed up more than a washbasin full of blood and died. At autopsy a bronchiogenic carcinoma was found in the left upper lobe.

#### SUMMARY

A series of cases illustrating various nontuberculous complications of calcified hilus lymph nodes is presented. The symptoms and the clinical and roentgenologic findings of this entity can simulate every type of acute and chronic bronchial and pulmonary disease. Basically, all of the findings are caused by bronchial ulceration, narrowing, and occlusion. The choice of treatment is decided on the basis of the nature and extent of the accompanying pulmonary infection.

#### SUMARIO

#### *Complicaciones No Tuberculosas Tardías de los Ganglios Linfáticos Calcificados del Hilos*

Preséntase una serie de casos que demuestran varias complicaciones no tuberculosas de los ganglios linfáticos calcificados del hilo. La semiología y los hallazgos clínicos y roentgenológicos pueden simular cuanta variedad existe de afección bronquial y pulmonar, ya aguda o crónica. En el fondo, todos los hallazgos son ocasionados por úlcera, estenosis y oclusión bronquial. La

selección del tratamiento se basa en la naturaleza y extensión de la infección pulmonar concomitante

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# OBSERVATIONS ON LOWER LOBE DISEASE IN PULMONARY TUBERCULOSIS<sup>1</sup>

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## INTRODUCTION

Some sixty years ago Kidd (1) and Fowler (2) recognized that the lower lobe could be the site of the initial reinfection lesion in pulmonary tuberculosis. Study in the ensuing years confirmed their observations. Particularly in the last two decades, judging by the increasing frequency of reports on this subject, there has been a growing interest in this phase of tuberculosis.

Recently the authors had a rather large cross section of pulmonary tuberculosis available, during a period of service at a former Army General Hospital<sup>2</sup>. With an interest in lower lobe disease, a study of the case files of the chest service at this hospital covering a three year period<sup>3</sup> was done. Its purpose was to observe the incidence and results of treatment in an all male group of military age as compared to the reports in the literature.

*Definition.* By pure anatomical definition, lower lobe would refer only to the posterior inferior lobes of the lung. However, at this institution the term was used to include the right middle lobe as well. From a practical point of view, disease in the right middle lobe presents problems comparable to those associated with basilar disease. Realizing that the lingula could be considered the left "middle lobe," the authors kept this anatomical factor in mind. In reviewing the following cases, no instance could be found where the initial lesion was demonstrated in this portion of the lung field.

The scope of this study has been confined to those cases with definite roentgenological evidence that the initial lesion occurred in the right middle lobe, or the right or left lower lobes. Likewise, in the cases considered from the standpoint of the results of treatment, the predominant involvement was in the lower lobe, even though serial films showed dissemination of a lesser degree to the upper lung fields.

## OBSERVATIONS

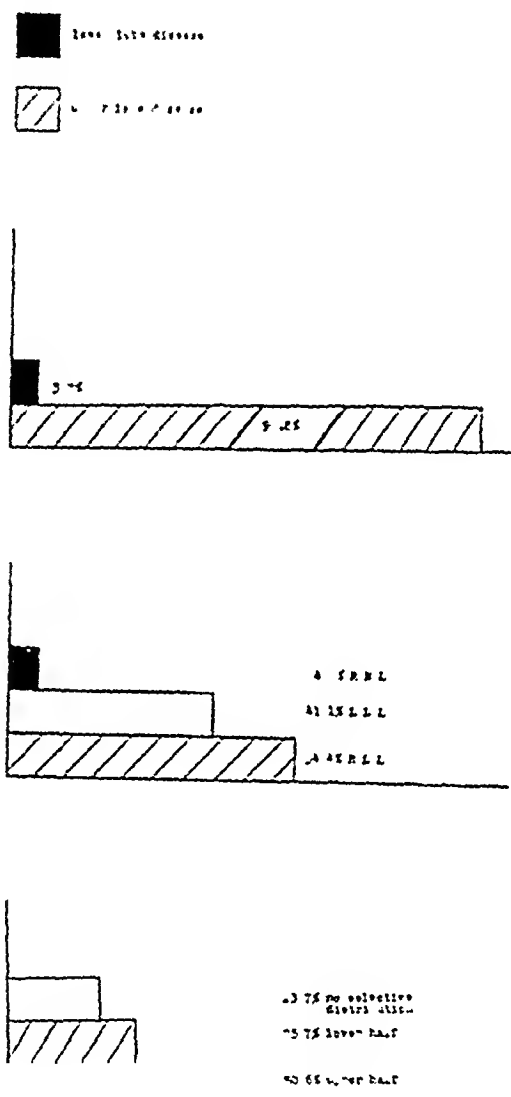
*General incidence.* A review was made of 2,784 successive cases of tuberculosis in which the diagnosis had been definitely established at the time of discharge or transfer from Bruns General Hospital. All of the patients were males. In 2,777 cases the tuberculosis was considered to be of reinfection type, in the remainder the infection was in the form of a primary complex. Guided by the foregoing definition, 90 cases of lower lobe disease were found. This represented 3.2 per cent of the entire group (figure 1). Eighty-five infections were classified as reinfection type, or 3.1 per cent of the total reinfection group.

<sup>1</sup> From the Bruns General Hospital, Santa Fe, New Mexico.

<sup>2</sup> Bruns General Hospital, Santa Fe, N. M.

<sup>3</sup> August, 1943 to August, 1946.

*Distribution of lesions* The majority of the lesions were in the right and left lower lobes. The right lower lobe was more frequently the site of initial involvement than the left lower lobe. In 19 of the 90 cases in the group, the disease



FIGS 1-3

FIG 1 Localization of lesion by lobe in 2,777 cases of tuberculosis

FIG 2 Ninety cases of lower lobe tuberculosis. Distribution of lesions between right middle and both lower lobes

FIG 3 Ninety cases of lower lobe tuberculosis. Localization of lesion within the lobe

first appeared in the right lower lobe and in 37 cases the first lesion was in the left lower lobe. The initial lesion occurred in the right middle lobe in only 4 instances (figure 2).

*Location of disease process within the individual lobe* This particular question

was studied to determine whether there was any selective distribution in lower lobe disease. Analysis as to whether the extent of the involvement was predominantly in the upper half or the lower half was carried out. Eighty-nine of the 90 case records presented sufficient information to permit this classification. The upper half of the lobe was involved twice as frequently as the lower half. Forty-six had upper lobe distribution. In contrast, 23 demonstrated lower half involvement. Of the remainder, 20 showed no specific selection but involved the entire lobe (figure 3).

*Radiopathological description* In 62 (72.9 per cent) of the reinfection cases, cavitory disease was evident on the first chest film obtained after hospitalization. In the remainder (27.1 per cent) only infiltrations were present. There was no unusual incidence of cavitation in any particular lobe.

Qualitatively, there was nothing characteristic of the infiltrations in the lower lobes. As might be expected, the majority (53) were interpreted as "mixed" disease. Twenty were considered to be "productive" and 5 "exudative". The only "calcific" lesions were the 5 primary complexes. The remaining records (7) were not classified in this respect.

*Race and age* As compared to the overall pulmonary tuberculosis census of the hospital, there was no difference in the incidence of lower lobe disease with regard to race or age. Similarly, there was no specific lobe distribution. The series included 18 Negroes, 2 Eskimos, and one Indian. The age range was 18 to 46 years, the average was 25 years.

#### RESULTS OF TREATMENT

The results of treatment were studied with reference to the factors of incidence and also the types of treatment used.

It was appreciated that the period of observation was short. The time ranged from one month to two years, the average being nine months to one year. As final military disposition divided this group into numerous destinations<sup>4</sup>, it was considered unlikely that final observation as a unit would ever be possible. Therefore, a report of the results observed in this relatively brief period of observation seemed justifiable.

#### *Results with Reference to Factors of Incidence*

*Relation to involved lobe* The lobe involved offered no prognostic clue. In 32 (65.1 per cent) of the 49 cases with right lower lobe involvement, the disease improved. There was no significant difference with the left lower lobe lesions which showed improvement in 26 of the 37 cases.

*Location of disease process within the individual lobe* The particular location of the lesion within the lobe was likewise of no prognostic value. Of 62 lesions that showed improvement, 32 (51.6 per cent) were located in the upper half of the involved lobe. The other 30 were equally distributed between those cases which

<sup>4</sup> Seventy-six of these patients were transferred to other sanatoriums to continue treatment, 5 were returned to duty with healed primary disease, and 9 separated from military service with inactive disease.



involved the lower half of the lobe and those cases with involvement throughout the lobe. Likewise, there was no apparent relationship between lack of improvement and location of the lesion within the lobe. In thirteen (61.9 per cent) of the 21 patients whose disease failed to improve, the predominant involvement was in the upper half of the lobe.

*Race* The tuberculosis had an unfavorable course in the 2 Eskimos in this group of patients. One had moderately advanced disease, the other far advanced. Both were treated only with bed rest. With this possible exception there was no correlation between the results of treatment and racial types.

*Age* No significant correlation was noted between the clinical course of the lower lobe disease and the age of the patient. The average age for those who improved was 21.6 years, with a range from 19 to 39 years. The average age for those with an unfavorable course was 25.8 years, with a range from 18 to 46 years.

### *Results Analyzed According to Types of Treatment*

*Method of Study* Three major groups could be defined, determined by the types of therapy in frequent use: (1) bed rest alone, (2) pneumothorax, and (3) lobectomy.

Several other procedures, pneumoperitoneum, phrenic nerve interruption, and the combination of these two, formed a miscellaneous group.

Each of these groups was divided into two categories: those cases showing improvement, and those cases showing no improvement (including progressive disease).

The criteria for improvement included one or more of the following points:

- 1 Clinical improvement, as judged by gain in weight, absence of fever, and decrease to absence of sputum and cough.
- 2 Roentgenological improvement as evidenced by study of serial roentgenograms.
- 3 Disappearance of acid fast bacilli from sputum examined after concentrations.

Individual reference was noted in the response of cavity disease to treatment. The group was studied with regard to size of cavity (diameter) prior to treatment, degree of cavity closure, and reversal of infectiousness.

*Comparison of results obtained by various methods of treatment* Improvement in the course of the disease occurred in 41 (71.9 per cent) of the 57 patients treated with bed rest alone, 13 (68.4 per cent) of the 19 treated with pneumothorax, and 6 (85.7 per cent) of the 7 patients in whom lobectomy was performed (figure 4).

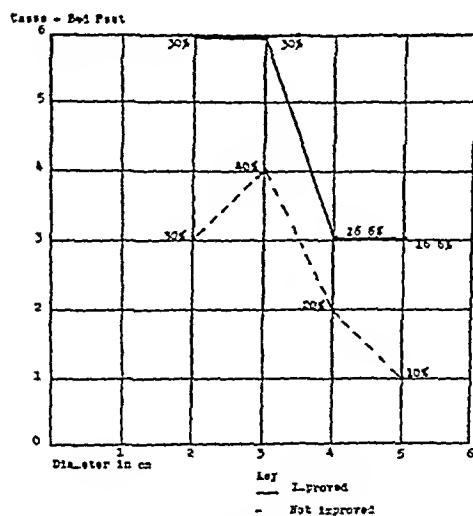
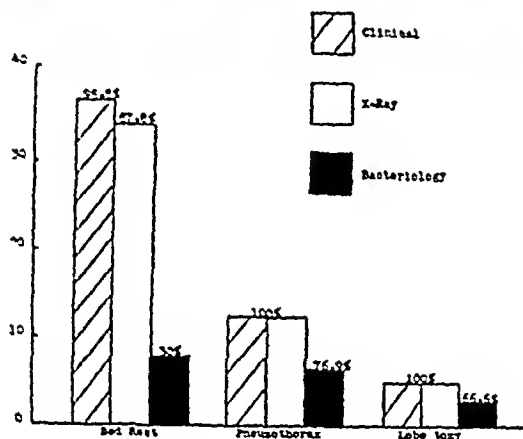
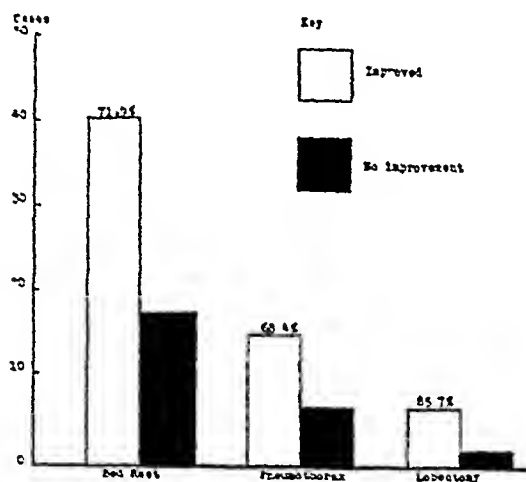
On study of the results of treatment with reference to the individual points mentioned under criteria for improvement, it was the writers' impression that pneumothorax and lobectomy effected a greater degree of improvement than bed rest alone. There was clinical as well as roentgenological improvement in the lesions of those 19 patients who showed improvement with pneumothorax or underwent lobectomy. Conversely, in only 36 (87.8 per cent) of the 41 cases in which improvement occurred on bed rest alone was there both clinical and roent-

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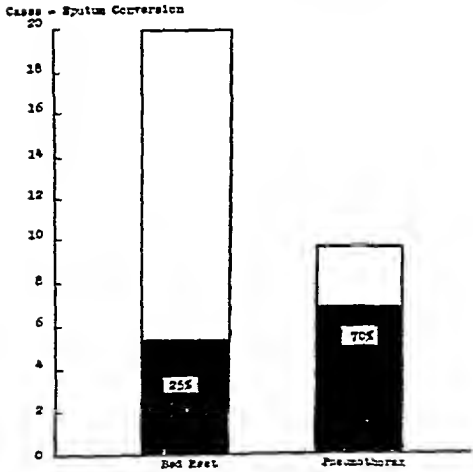
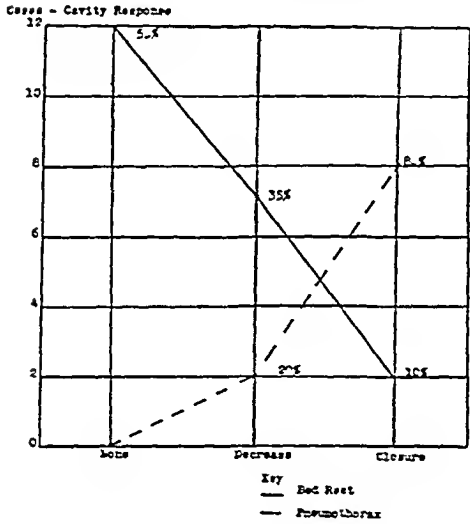
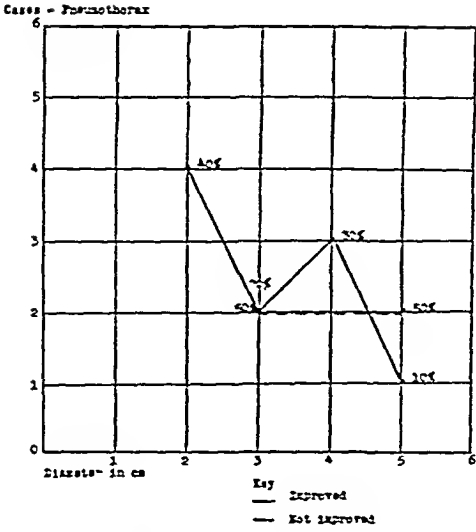
FIG 4 Results of three forms of treatment of 90 cases of lower lobe tuberculosis

FIG 5 Clinical, roentgenologic and bacteriologic results of three forms of treatment of lower lobe tuberculosis

FIG 6 Lower lobe tuberculosis. Change in cavity diameter under treatment by bed rest



FIGS 4-6



FIGS 7-9

genological improvement Of the remainder of this "bed rest" group only clinical improvement was observed in 3 cases and only roentgenological evidence of improvement in two others

In all of the cases in the pneumothorax and lobectomy groups the sputum was positive for tubercle bacilli prior to treatment Tubercle bacilli disappeared from the sputum in 10 of the 13 patients whose disease improved with pneumothorax and in 4 of the 6 with improvement after lobectomy In the "bed rest" group, 30 of the 41 patients whose disease improved had tubercle bacilli in the sputum on the initial examination, and in 9 of the 30 the sputum subsequently was negative for tubercle bacilli (figure 5)

*Response of Cavitory Disease* There were 48 patients with cavitory disease The diameter of the cavity was recorded in 42 cases It ranged from 2 to 5 cm The average was 3.1 cm

There was no correlation between size of cavity and therapeutic response Twenty-eight cases were treated by only bed rest, 18 improved, 10 did not improve Twelve of those that improved and 7 of the unimproved cases had an average range in cavity diameter of 2 to 3 cm The remainder of each group had a range of 4 to 5 cm (figure 6) The cavity diameter in 6 of the 10 cases that improved with pneumothorax ranged between 2 to 3 cm, in the remainder, the cavities were 4 to 5 cm in diameter In 2 of the 4 patients whose disease failed to improve, cavities 3 cm in diameter were present, and in the other 2, the cavities were 5 cm in diameter (figure 7)

Pneumothorax appeared to be more effective in obtaining cavity closure and sputum "conversion" than bed rest alone Cavity closure occurred in only 2 of the 20 cases of cavitory disease in which improvement occurred on bed rest, while this objective was attained in 8 of the 10 cases that received pneumothorax Sputum "conversion" occurred in 5 cases treated only with bed rest and in 7 of the pneumothorax cases (figures 8 and 9)

*Pneumoperitoneum and phrenic interruption* Pneumoperitoneum and phrenic interruption were used in only 5 cases Possibly one of the reasons why these procedures were not used more frequently was that the consensus of opinion at the weekly chest conferences, where therapy for the cases was discussed and decided, did not favor these procedures with the same enthusiasm as might be held by others

Three patients with cavitory disease were selected for pneumoperitoneum In one diaphragmatic paralysis was present and, in the others, no phrenic interruption was performed The cavity diameter ranged from 2.5 to 4 cm All cavities were located in the upper half of the left lower lobe None of the cases demonstrated any improvement after four to six months of observation under such therapy

Another 2 received phrenic interruption alone Both had cavity diameters of

FIG. 7. Lower lobe tuberculosis. Comparison of change in cavity diameter after treatment with bed rest or pneumothorax.

FIG. 8. Lower lobe tuberculosis. Comparison of change in cavity diameter after treatment with bed rest or pneumothorax.

FIG. 9. Bacteriologic results of treatment with bed rest or pneumothorax.

the upper half of the left lower lobe, and the cavities ranged from 2 to 3 cm in diameter. No change in the status of the disease was noted after approximately four months of therapy.

### DISCUSSION

In this study the general incidence (3.1 per cent) of reinfection type of lower lobe disease compared favorably with other reported studies. According to Romendick, Friedman and Schwartz (3), the incidence may vary from 0.003 per cent to 18.3 per cent. In their own series of 2,354 cases, 63 (2.7 per cent) had lower lobe disease. Lathrop and Lyman (4) found an incidence of 3.1 per cent, 83 cases in a series of 2,809 cases. On the other hand, Reisner (5) reported only 0.8 per cent lower lobe involvement, 34 cases in a series of 4,494 cases.

Incidence of the lower lobe most frequently involved in the present series compared favorably with the previous reports. In 54.4 per cent of the present series, the involvement was in the right lower lobe. Romendick *et al* (3) reported 58.7 per cent with involvement of the right lower lobe and Hawkins and Thomas (6), and Sokoloff (7) also found the right lower lobe more frequently involved.

The greater frequency with which tuberculosis occurred in the upper half of the lower lobe has also been noted in other studies. Ossen (8) observed that lesions occurred in the apex of the lower lobe more frequently than in the basilar portions. Sokoloff (7) reported 10 lesions located close to the root of the lung or in the upper third of the lower lobe. One of the factors in the pathogenesis of this localization might be found in the work of Sweany, Cook and Kegerreis (9). They studied the position of primary cavitation in pulmonary tuberculosis and found that the apices of the lower lobes frequently contained the oldest lesion in the anatomical specimen. Viswanathan (10) discussed the physiologic interpretation of the apical localization and believes it represents a predisposition to disease because of inadequate ventilation and poor circulation in the upper portion of the lower lobe.

The tendency for lower lobe tuberculosis to become cavitory disease (72.9 per cent of the cases in this series) is emphasized in other reports in the literature. Reisner (5) commented that the majority of his cases had cavernous disease. Sokoloff (7) observed in his series that there was a tendency for rapid development of cavernous disease.

The age range, 18 to 46 years, with an average of 25 years, followed closely the ranges stated by other writers on this subject. Romendick *et al* (3) reported that 91.5 per cent of their cases were under 40 years of age. In Reisner's group two-thirds were between the ages of 17 and 30 years, and Viswanathan (10) reported a range of 17 to 42 years. Like this study, Romendick *et al* (3), Reisner (5), and Weidman and Campbell (11) could find no definite relationship between the race of the patient and the incidence of lower lobe disease. Though this series included only males, a greater incidence in females is reported in the literature (5, 10, 11).

Weidman and Campbell (11) reported 6 cases treated by only bed rest. Four obtained a satisfactory result, 2 had cavitory involvement. Although improve

ment was noted in 71.9 per cent of the cases in the present study treated with bed rest, in only 15 of 57 cases was the response satisfactory with clinical and roentgenological improvement and sputum "conversion." Only 2 of this group of 15 had cavity disease.

There has been considerable difference of opinion as to the choice of collapse procedure. Pohl (12) mentioned pneumothorax as the preferred treatment. In contrast, Hawkins and Thomas (6) reported pneumothorax ineffective in 11 of 15 cases of lower lobe tuberculosis. Weidman and Campbell (11) stated that 6 of 15 cases treated by pneumothorax obtained a satisfactory result. Reisner (5) reported pneumothorax effective in 58 per cent of his cases, 11 in a series of 19. Of the 19 cases in the present study, 13 showed improvement, and 10 had a satisfactory result (clinical and roentgenological improvement with sputum "conversion").

Phrenic interruption and pneumoperitoneum were ineffective in the 5 cases in which it was used. Hawkins and Thomas (6) contrasted their poor results with pneumothorax with the response, including cavity closure, noted in 10 cases treated by phrenic interruption and pneumoperitoneum. They emphasized the ineffectiveness of phrenic interruption unless supplemented by pneumoperitoneum. The results of Weidman and Campbell (11) and Reisner (5) supported this opinion. The former reported that all 4 cases in their series treated by phrenic paralysis had poor results. Reisner (5) found phrenic interruption effective in only one of 8 cases so treated.

Carr and Harter (13) recommended pulmonary resection for that group of patients without reasonable hope of cure by collapse therapy. In this group they also included lower lobe disease not amenable to collapse treatment. In a series of 60 resections by Overholt and Wilson (14), 10 were lower lobe disease. All were improved or became clinically well after the procedure although in 5 the sputum was positive for tubercle bacilli when the cases were reported. In Bailey's (15) series of 80 resections, 4 were for lower lobe disease, 2 were improved. In the lobectomy group discussed in this paper there were 7 patients. Six improved or became clinically well, 2 of these patients had persistently "positive" sputum postoperatively.

In addition to resection, the use of thoracoplasty for lower lobe disease has been discussed in the literature (3, 7, 16). Freeland (16) suggested its use in persistent basal cavities. Romendick *et al* (3) reported 4 cases by thoracoplasty, only one became arrested.

### SUMMARY

Observations on lower lobe involvement in pulmonary tuberculosis are reported. The source of the material consisted of 2,784 successive admissions for pulmonary tuberculosis at an Army General Hospital.

1. Lower lobe disease was found in 85 cases or 3.1 per cent of the group.
2. Disease of the right lower lobe was slightly more frequent than of the left lower lobe.
3. The upper half of the involved lobe became the initial focus of the disease more often than the basilar portion.

4 There was a tendency for rapid development of cavitary disease

5 Pneumothorax and lobectomy were effective therapeutic adjuncts in this group of cases

### SUMARIO

#### *Observaciones Relativas a la Enfermedad del Lóbulo Inferior en la Tuberculosis Pulmonar*

Estas observaciones referentes a la invasión del lóbulo inferior en la tuberculosis pulmonar proceden de 2,784 ingresos sucesivos por tuberculosis pulmonar en un Hospital General del Ejército E U A

1 Descubrióse afección de los lóbulos inferiores en 85 casos, o sea 3.1 por ciento del grupo

2 La enfermedad del lóbulo inferior derecho fué ligeramente más frecuente que la del izquierdo

3 La mitad superior del lóbulo afectado se convirtió en foco inicial de la enfermedad más a menudo que la porción basal

4 Observóse tendencia a rápida formación de cavernas

5 En este grupo el neumotórax y la lobectomía mostraron su efectividad como coadyuvantes terapéuticos

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# INSULIN IN THE TREATMENT OF TUBERCULOUS PATIENTS WITH ANOREXIA—A MODIFIED TECHNIQUE.<sup>1</sup>

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## INTRODUCTION

The use of insulin for the treatment of anorexia and undernutrition in tuberculous patients was widely discussed in both the European and the American medical literature from 1923 on through the late thirties (1, 2, 3, 4, 5, 6, 7, 8). Although the majority of authors reported favorable results, others claimed that it produced no constant or lasting gain in weight and did not alter the course of the disease. Furthermore, they warned of possible deleterious effects of hypoglycemia on the tuberculous process, particularly in cases of exudative disease. The proponents of insulin therapy failed apparently to present a sufficiently convincing case and, instead of becoming widely accepted, the method gradually fell into disuse.

During World War II several thousand cases of anxiety neurosis were treated with sub-shock doses of insulin (9, 10) and attention was again called to its efficacy in improving appetite and nutrition. Insulin was also found to have a noticeable sedative action. "Symptoms of acute anxiety, tremor, perspiration, restlessness, and insomnia will tend to improve toward the end of the first week" (Kelly and Thompson (11)).

The idea of using insulin in sub-shock doses to promote weight gain in anorexic tuberculous patients was suggested to the present writers by Dr. Irving Pine of Asheville, North Carolina, who had noted the enormous weight gain of psychiatric patients receiving large doses of insulin.

It is not difficult to understand why many a patient in a tuberculosis hospital develops anxiety. He is aware of the fact that he has a serious chronic disease and he may actually have seen or known others who have died of this disease. He worries about his family and how they will manage financially during his prolonged illness. He wonders whether he will be able to return to his job and his friends after recovery, or whether he will be regarded as an outcast. The mention of "thoracoplasty" produces fear of mutilation and death. Pneumothorax and pneumoperitoneum mean the dreaded needle and the complications of which he has heard the other patients talk. A previous hemoptysis or a spontaneous pneumothorax may further have implanted the overpowering fear of suffocation. This continued emotional stress helps to explain why some tuberculous patients will continue to eat poorly and lose weight even after all fever has gone and the

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pulmonary disease shows clinical and radiologic improvement. The habit of anorexia has been established and must be broken. Insulin treatment is of value in "breaking down the vicious cycle of anxiety and loss of weight" (9).

## OBSERVATIONS

### *Technique*

Until now the only way in which insulin has been used to produce weight gain has been in small doses given at fairly short intervals before feedings. The technique used in this study consisted of giving regular insulin subcutaneously in single daily doses, increased daily by 5 or 10 units from a starting level of 20 units to as high as 50 or 60 units. This final figure has been found to be effective in most patients and is continued for a total period of one to two months. The insulin is given to the fasting patient at 6 00 a m. and no food is taken until breakfast is served at 8 00 a m., by which time a voracious appetite has been aroused and occasionally a feeling of faintness. A normal hospital meal schedule is resumed for the noon meal at 11 30 a m. and supper at 5 00 p m. It has been found that the increased appetite created for breakfast survives to a lesser degree for the other meals.

### *Composition of Clinical Series*

Sixteen white male veterans at Oteen Veterans Administration Hospital, ranging in age from 18 to 35 years, were treated as described. These men had been hospitalized at Oteen for periods of six months to four years and all of them had received one or more of the following forms of collapse therapy: pneumothorax, pneumoperitoneum, phrenic crush, thoracoplasty, and extrapleural lucite pack. All were afebrile, showed stationary or slowly regressing disease, and complained of poor appetite for the past two to six months.

## RESULTS

Of the 16 patients treated with insulin in sub-shock doses, all registered some gain in weight. Nine gained between ten and twenty pounds, and 7 gained from two to nine pounds, in a period of four weeks. Follow-up observations for six to eight weeks after insulin was discontinued show that one-half of the patients lost approximately 25 per cent of the weight they had gained. Five patients either maintained their gain in weight or added further weight. Three patients left the hospital "AWOL" and their progress could not be followed. All of the 13 patients who remained in the hospital agreed that their appetite now was definitely better than it had been prior to receiving insulin. In none of the patients treated was any definite exacerbation of the tuberculous process noted either during or six to eight weeks after the course of insulin therapy.

The following case reports are illustrative of the clinical course observed during insulin therapy.

## CASE REPORTS

*Case 1* M. D., a 35 year old man with known pulmonary tuberculosis for one year, complicated by left pleural effusion, was treated with bed rest and pneumoperitoneum. His appe-

tite was poor, particularly at breakfast, at which time he would usually take only a cup of coffee and a small amount of milk. During rest hour he would fidget about in bed and his legs would jerk aimlessly. He complained of frequent heartburn. He was started on 20 units of regular insulin which was increased by 10 units daily up to 50 units once a day. Beginning on the second day of treatment there was a noticeable increase in appetite, most marked at breakfast but to a lesser extent also at the noon and evening meals. For breakfast the patient was now able to eat four eggs, five or six slices of toast, a glass of fruit juice, a bowl of cereal with a glass of milk and a cup of coffee. He also noted a definite sedative action. He slept and rested better and his feet stopped "jumping." He gained 8 pounds in a little less than a month.

*Case 2* B F was a 24 year old man with known tuberculosis for over three years, complicated by tuberculous laryngitis which was healed at the time of insulin therapy. He had fibroexudative disease scattered throughout both lungs, which was satisfactorily treated by a combination of left pneumothorax and pneumoperitoneum. For about a year before treatment his weight remained constant at about 20 pounds below his normal level. In late November 1947, he began to complain of early morning nausea which grew gradually worse until no appreciable amount of food was tolerated by mouth. All methods, including intravenous feeding, were tried without breaking through the vicious cycle. In January 1948, insulin was tried, the response was rapid and dramatic. The acute episode was aborted and a ravenous appetite resulted in a gain in weight from 144 to 164 pounds in a little less than two months.

*Case 3* W R was an 18 year old adolescent who had had tuberculosis for one year. Sputum was positive for tubercle bacilli at the onset, but converted with a right pneumothorax after an open pneumonolysis had been performed. This patient presented a great behavior problem, having had no adequate discipline and guidance. He came from a small town in Kentucky where almost the only type of occupation available was work in the mines or the sawmills, and he felt that his pulmonary disease would prevent him from handling these jobs. His horizon extended no further. He was extremely tense, nervous, anxious, and insecure. His appetite was very poor, with no response to any medical measures. Insulin treatment resulted in the creation of an enormous appetite and a gain of 17 pounds in weight in one month.

*Case 4* F H was a 22 year old man with known tuberculosis for seven months, which had been adequately treated with left phrenic crush and pneumoperitoneum, with consequent reversal of infectiousness. The patient claimed that he had been a "good eater" before entering the hospital. For the previous six months, however, he had suffered from "nervous stomach", poor appetite, and occasional diarrhea. Medical measures to stimulate appetite were of no avail. Insulin resulted in a prompt and marked improvement in appetite and a gain in weight of from 117 to 127½ pounds in one and one-half months.

*Case 5* W A was a 24 year old veteran with known cavity tuberculosis for four years, which had been treated first with left phrenic crush and pneumoperitoneum and then, in 1947, with a left extrapleural lucite pack which failed to close the cavity. Less than a year later the lucite balls were removed and a thoracoplasty was performed. This man had been extremely anxious over the long course of his disease without much improvement, and was very irritable and fretful. Under insulin therapy his mental outlook became dramatically better, he was cheerful and cooperative, and he gained 13½ pounds in a little less than one month's time.

*Case 6* J P was a 31 year old veteran with known far advanced pulmonary tuberculosis for over five years, who had been treated successively with right pneumothorax, right thoracoplasty, left pneumothorax, and pneumoperitoneum. The patient's chronic illness had re-

sulted in a weight loss that remained persistently at about 60 pounds below his normal level. For ten days he was given sterile water injections but was otherwise treated just like the other insulin patients. This resulted in no subjective improvement and he lost one pound. On starting insulin in the second week the patient noted at once the effect on his appetite and he gained 5 pounds in two weeks.

TABLE 1  
*Weight Data on Patients Treated with Insulin*

	I	II	III	IV	V	VI	VII
	Normal weight	Weight on admission	Lowest weight recorded during illness	Weight before treatment	Weight after one month of treatment	Net gain	Weight 6 to 8 weeks after end of treatment
	pounds	pounds	pounds	pounds	pounds	pounds	pounds
M D (1)	150	153	139	143	151½	8½	153
B F (2)	165	155	144	144	164	20	160
W R (3)	120	112	109	109	126	17	AWOL
F H (4)	135	120	117	117	127½	10½	126½
W A A (5)	145	135	87	101	114½	13½	114
J P (6)	165	165	104	117½	123	5½	124
J E M (7)	140	135	119	127	138	11	134½
L B (8)	160	144	118	124	140	16	140
M C (9)	145	139	132	135	140	5	AWOL
R C (10)	143	129	119	133½	145	11½	AWOL
R H (11)	155	98	98	122	130	8	128
J S (12)	157	147	140	146	148	2	148
J M (13)	132	117	110	110	120	10	117
H G (14)	160	113	112½	112½	126	13½	128
F M (15)	165	139	137	139	142½	3½	141½
P D (16)	145	120	119½	119½	126	6½	122

*Case 7 J M*, a 37 year old man with known pulmonary tuberculosis for five years, was treated successively with right pneumothorax, left pneumothorax, right phrenic crush, and pneumoperitoneum, and finally with right thoracoplasty and streptomycin. His appetite had fallen off just before the chest surgery and his weight had dropped from 140 to 127 pounds. He admitted that prior to the thoracoplasty he had worried a great deal about the possible physical deformity resulting from the operation. Furthermore, he had sustained some disturbance of vestibular function as a result of streptomycin treatment and was much concerned about his persistent dizziness. On insulin therapy this man gained 11 pounds in one month.

The pertinent weight details on all 16 patients treated with insulin may be seen in table 1.

#### DISCUSSION

The method of use of insulin in these underweight and anorexic tuberculous patients differs in two major respects from that heretofore employed. In the past it has been the uniform practice to give small doses (3 to 20 units) from twenty to forty-five minutes before meals, two or three times a day. In the present study single, daily, relatively large (50 to 60 units) "sub-shock" doses

have been given on an empty stomach in the early morning with breakfast served about two hours later.

This higher dose and the delay between injection and feeding usually allow the blood sugar to fall to about 75 per cent of its normal value. It is well established that a 25 per cent fall in blood sugar level will induce marked gastric secretion and motility (12, 13). It is interesting that physiologists have long known that these effects require at least seventy-five to ninety minutes to reach their peak, yet most clinical investigators in reporting the use of insulin for appetite stimulation have allowed only twenty to forty-five minutes between injection and feeding, which has not permitted maximum benefit. In the present study, the patients' appetite and hunger increased to a peak at about two hours after injection, succeeded by faintness if food was withheld. By serving food when the subjective desire for it was greatest, a very satisfactory increase in food intake was achieved.

In addition to stimulating hunger through increased gastric secretions and contractions, insulin in sub-shock doses may also contribute toward weight gain by its sedative effect on the patient. Most of the subjects noted a definite decrease in their restless fidgeting in bed and useless activity on the ward. Some were able to reduce or dispense with sedative drugs which they had been taking rather regularly. A few showed marked improvement in general outlook, with disappearance of many vague hypochondriacal complaints. In this connection, however, it is necessary to emphasize the fact that, in the presence of well-established personality disorders, no fundamental change can be expected from sub-shock doses of insulin (11, 11).

The duration of the course of treatment with insulin was arbitrary. The patients were treated for one to two months, but courses lasting several months or repeated courses of one or two months with a month off in between have been used with the old technique (6). This seems to be a matter of individual adjustment. There is little to be gained from continuing the course after the patient has reached his previous normal level of weight or when he has become stabilized and ceases to gain further. If pushed up beyond his normal level, the absolute increment is apt to be lost as soon as treatment is terminated.

In any regimen of treatment, the role of suggestion is not to be underestimated. It has indeed been claimed (15) that insulin could not do more for anorexia and undernutrition than would a good diet and ample encouragement. In the cases here described, however, the diet was constant before, during, and after treatment, and suggestion, as well as miscellaneous medical measures (vitamins, "tonics," et cetera), had been tried without success. We feel that the insulin regimen abruptly breaks through a habit pattern of worry and chronic poor appetite, resulting in immediate weight gain (14, 16). The immense psychic boost of knowing that one is gaining weight and presumably getting generally better plays a considerable part, once the treatment is well under way, in perpetuating the weight gain, maintaining better appetite after treatment, and improving the whole mental outlook. In one case cited, suggestion combined with sterile water injections were used for ten days with no improvement (the weight dropped one pound), but when insulin was substituted for sterile water (unknown to the patient) an increase in appetite was noted at once with resultant gain in weight.

It has been suggested at various times that the weight gain of insulin-treated patients consists largely of water retention, and as such is of no lasting value. Careful studies of water balance (17), however, show that this is not the case.

Some writers (18, 2) have voiced warnings about possible deleterious effects of insulin in nondiabetics. The suggestion that it might induce disturbance of normal endocrine functions through suppression of islet cell activity has never been substantiated, and Allen (19) states categorically that he has heard of no instance of development of diabetes or of any other endocrine disorder. In the past, insulin has been given over extensive periods for many months, either continuously or in repeated courses, with no ill effects observed (20, 21). In a disease like tuberculosis, the principal deterrent to the use of insulin has been the fear that hypoglycemia may initiate exacerbations of exudative lesions. The mechanism of such exacerbation has never been clearly described and the feeling seems to be based on a few isolated reports of spread or hemorrhage while under insulin therapy. Closer scrutiny reveals that these were usually cases of active exudative or cavitory disease, in a certain number of which spreads and hemoptyses may be expected to occur with any type of treatment. No study has ever proved that the incidence of such complications was any higher in the insulin-treated series than in a comparable nontreated group. Nevertheless, however dubious the danger may be, it is one that cannot be absolutely excluded. Therefore, the patients for this study were chosen, not as a cross-section of tuberculosis sufferers, but as those most likely to be benefited, omitting all who might conceivably be adversely affected by insulin. The group chosen consisted of fairly young men who were afebrile, in whom tuberculosis was either stationary or gradually improving, who were anorexic and considerably below their normal weight, and who had not shown any tendency to gain weight under conservative management. Those excluded were patients with active exudative pulmonary disease, patients with definite tuberculous enteritis, patients over 45, those with organic heart disease, and those who displayed sensitivity to insulin. All patients treated were under close supervision, and adequate materials were kept at hand for prompt oral or intravenous administration of glucose in case of insulin shock. With the doses used, no instance of insulin shock has been encountered in the present group of patients.

#### SUMMARY AND CONCLUSIONS

- 1 The use of regular insulin in sub-shock doses to stimulate appetite and weight gain in anorexic tuberculous patients has been discussed.

- 2 The element of anxiety is an important factor in the mechanism of anorexia in these cases.

- 3 Sixteen patients were treated for one month with single daily doses of 50 units of insulin. Weight gains were recorded in all patients, and 9 gained between 10 and 20 pounds.

- 4 It is believed that in properly selected cases of quiescent tuberculosis, where anorexia and failure to gain weight are a prominent part of the clinical picture, insulin in sub-shock doses is a valuable adjunct in treatment, and is without any appreciable danger.

## SUMARIO Y CONCLUSIONES

*La Insulina en el Tratamiento de los Tuberculosos Anoréxicos—Técnica Modificada*

1 Discútese el empleo de la insulina corriente a dosis sub-choque para excitar el apetito y aumentar el peso en los tuberculosos con anorexia

2 El elemento de ansiedad es un importante factor en el mecanismo de la anorexia en estos casos

3 Dieciséis enfermos fueron tratados por un mes con dosis diarias únicas de 50 unidades de insulina, notándose en todos aumento de peso, que en nueve representó de unos 4.5 a 9 kg

4 Parece que, en casos debidamente seleccionados de tuberculosis quiescente, en los que la anorexia y la falta de aumento de peso constituyen parte destacada del cuadro clínico, la insulina a dosis de sub-choque es un valioso coadyuvante terapéutico sin que entrañe riesgo apreciable

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# TUBERCULOSIS OF THE TRACHEA AND MAJOR BRONCHI<sup>1</sup>

Results of Treatment with Streptomycin

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## INTRODUCTION

Tracheobronchial tuberculosis has received much attention in recent years. It is recognized as a frequent complication of pulmonary tuberculosis and is a serious problem which significantly alters the prognosis of the pulmonary disease. Treatment frequently must be modified when a tracheal or bronchial lesion is demonstrated.

Bronchoscopic examination is essential to the diagnosis of tracheobronchial tuberculosis and ideally should be performed on all patients admitted to sanatoriums because of tuberculosis. Certainly it is indicated before any form of collapse therapy is instituted and whenever there are symptoms of bronchial obstruction, such as wheezing respiration, bouts of fever, or persistent cough with retention of secretions. Tuberculous tracheobronchitis should be suspected when the symptoms are out of proportion to those which are likely to be caused by the findings on the roentgenogram of the chest, when the roentgenograms reveal evidence of atelectasis, or when the sputum remains positive for tubercle bacilli without obvious reason.

Preliminary reports of the treatment of tuberculous laryngitis and tuberculous ulceration of the trachea and major bronchi with streptomycin have been most encouraging (1, 2). Ulcers of the larynx and tracheobronchial tree were reported to have healed with amazing rapidity in the few cases in which such treatment was carried out. It was feared that results would be less dramatic when a larger series of patients were treated with streptomycin. The experience of the Veterans Administration (3), however, has amply confirmed the earlier impression that ulceration of the larynx, trachea, and major bronchi responds most satisfactorily to treatment with streptomycin. The report from the Veterans Administration stated that the ulcers of all of the 81 patients treated had healed. Brewer and Bogen likewise have reported similar results in 44 cases (4).

The question of the permanence of cure in cases of ulceration of the tracheobronchial tree is a matter of great importance. The Veterans Administration reported only one recurrence in the series of 81 cases. Brewer and Bogen (4) recorded recurrence in 3 cases in a relatively brief period of follow-up. It is the purpose of this report to describe the results in 3 of the earliest cases of tracheal and bronchial ulceration in which treatment with streptomycin was employed. These patients have remained under close observation for from one and one-half to three years since treatment was completed.

<sup>1</sup> From the Division of Medicine, Mayo Clinic, Rochester, Minnesota.

## REPORT OF CASES

*Case 1* A student nurse, aged 21 years, registered at the Mayo Clinic for routine annual physical examination on April 8, 1943. Routine roentgenograms of the chest revealed a minimal tuberculous lesion in the upper part of the right lung (figure 1a). Roentgenograms in 1940 and 1942 had revealed no abnormality. The patient was sent to Mineral Springs Sanatorium in May 1943. Tubercle bacilli were demonstrated by inoculation of guinea pigs with material obtained from the stomach during fasting. Treatment consisting of rest in bed was carried out and the appearance of the lesion improved progressively. The patient was dismissed from the sanatorium on June 5, 1944. Reactivation of the lesion was noted on a roentgenogram made in December 1944, and she was readmitted to the sanatorium. At this time moderately advanced tuberculosis of the upper part of the right lung and a small minimal lesion on the left were present. Pneumothorax was instituted on the right side. After collapse, apparent atelectasis of the right upper lobe was noted (figure 1b). The patient complained of wheezing respiration, and bronchoscope examination was carried out in March 1945. Ulceration was noted in the right main bronchus and on the right lateral aspect of the lower part of the trachea (figure 2). There was a definite stricture of the right main bronchus.

The patient returned to the clinic and was hospitalized in March 1945. Treatment with 0.5 Gm of streptomycin aerosol daily and 1.2 Gm of streptomycin by intramuscular injection daily was instituted. She remained under treatment for one month. Subsequent bronchoscope examinations showed progressive improvement with healing of ulceration and inflammatory reaction within five weeks after therapy was begun. After her return to the sanatorium in April 1945, 2 Gm of streptomycin were given intramuscularly each day for the next three months.

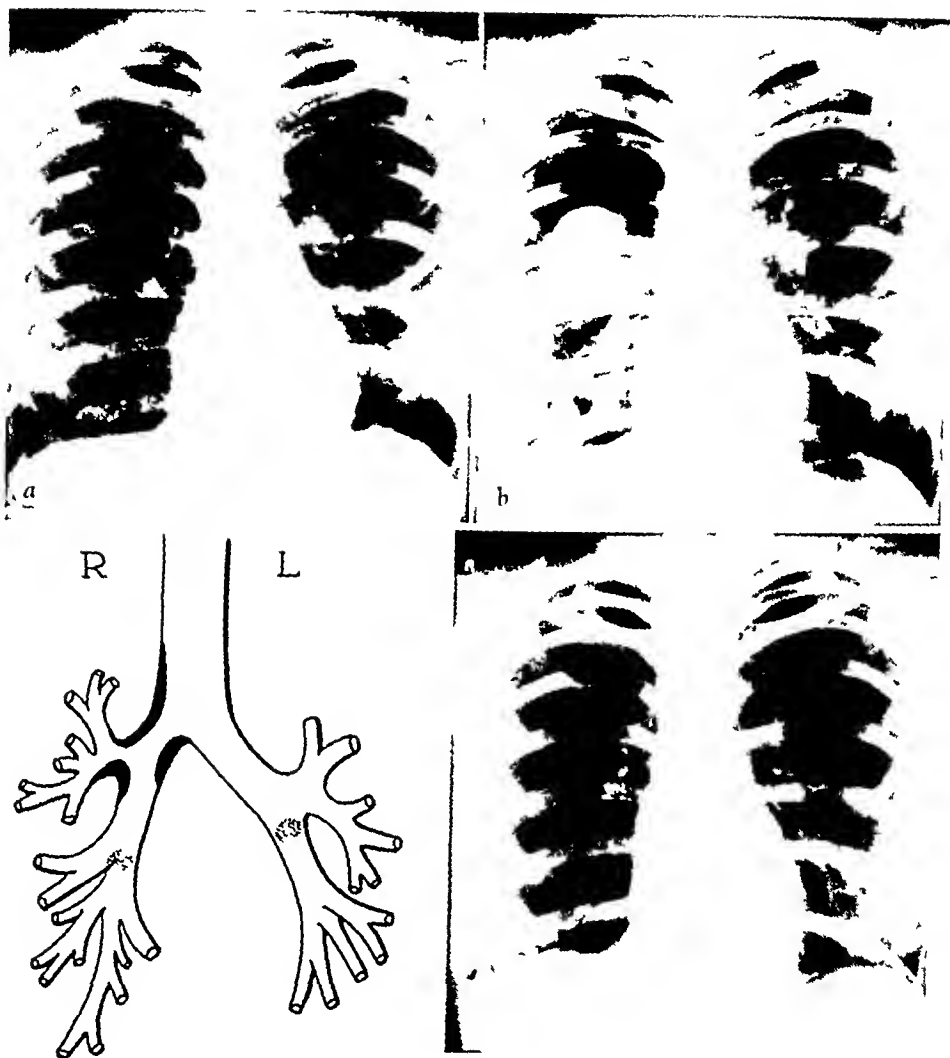
Bronchoscope examination has been repeated at regular intervals in the past three years and there has been no return of ulceration. A stricture of the right main bronchus reduces its lumen to half normal size. The atelectasis of the right upper lobe disappeared, however, when the pneumothorax was discontinued (figure 3). The patient returned to the school of nursing in July 1947, and was working full time in July 1948, over three years since apparent healing of the bronchial tuberculosis. Repeated cultures of gastric contents obtained during fasting have been negative for tubercle bacilli.

*Case 2* A woman, 37 years old, registered at the clinic on November 15, 1945. In the three years prior to coming to the clinic she had had several episodes of cough, wheezing, and difficult respiration. She had spent two years in a sanatorium because of tuberculosis. Although the roentgenogram revealed only a minimal lesion at the apex of the left lung (figure 4), her sputum was consistently positive for tubercle bacilli. Bronchoscope examination performed at the sanatorium one year previous to her visit to the clinic had revealed a tuberculous lesion of the left main and left upper lobe bronchi. Treatment had consisted of local application of 30 per cent silver nitrate. Although subsequent examinations showed evidence of improvement, the sputum had remained positive for tubercle bacilli and symptoms of bronchial obstruction had recurred.

General examination revealed nothing of significance except for a slight wheezing respiration. Direct smears of the sputum revealed acid-fast bacilli. The sedimentation rate was 60 mm in one hour (Westergren). At bronchoscope examination, a nodular ulcerating lesion was found on the left lateral wall of the trachea just above the carina (figure 5). Considerable granulation tissue was removed.

The patient was admitted to the hospital where streptomycin therapy was administered for sixty-four days. One gram was given by intramuscular injection each day and 0.5 Gm by nebulization. Bronchoscope examinations were performed at intervals of two weeks. Improvement was rapid and progressive. After a month of treatment the tracheo-bronchial tree was practically normal except for slight distortion of the orifice of the left main bronchus. Repeated bronchoscope examinations have been carried out ever since and her improvement has been maintained.





FIGS 1-3

FIG 1 (case 1) a (Upper left) April 8, 1943, minimal active pulmonary tuberculosis at the level of the second interspace anteriorly in the right lung b (Upper right) February 9, 1945, right pneumothorax for reactivated pulmonary tuberculosis Atelectasis of right upper lobe Minimal tuberculous lesions at the level of the second interspace anteriorly in the left lung

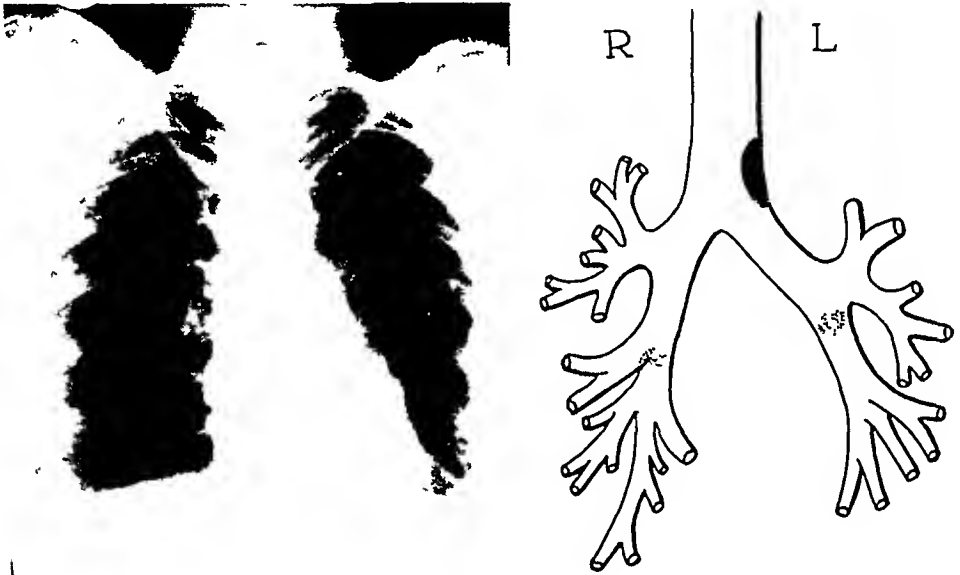
FIG 2 (case 1) (Lower left) The bronchial tree Areas marked with heavy black ink indicate distribution of tuberculous tracheobronchial lesions visualized at bronchoscopic examination

FIG 3 (case 1) (Lower right) November 13, 1945 Five months after streptomycin therapy was discontinued Chest negative except for residual linear fibrosis right upper lung field

Daily examinations of sputum were carried out during treatment Tubercle bacilli were found for two weeks after therapy was instituted but since then the sputum has been consistently negative Guinea pigs inoculated with her fasting gastric content on several occasions since treatment have not developed tuberculosis Sedimentation rate has

dropped to 18 mm per hour. There has been no evidence of recurrence of tuberculosis up to the present time (July 1948), two years and seven months since the bronchial lesion appeared to have healed.

**Case 3.** A nurse, 46 years of age, registered at the clinic on September 10, 1946. Pulmonary tuberculosis and tuberculous laryngitis had developed in 1932. After several months of rest in bed and silence therapy, the tuberculosis was considered arrested and she returned to her work as a nurse. She remained well until May 1946, when a routine roentgenogram of the chest revealed reactivation of tuberculosis in the apex of the left lung. Rest in bed was advised. The sputum contained tubercle bacilli. Toward the end of May 1946, wheezing, dyspnea, and pain in the throat developed. Bronchoscopic examination revealed an ulcerative process in the lower part of the trachea and in the right main bronchus,



Figs 4-5

FIG 4 (case 2) (Left) November 16, 1945, minimal tuberculous lesion in apex of left lung

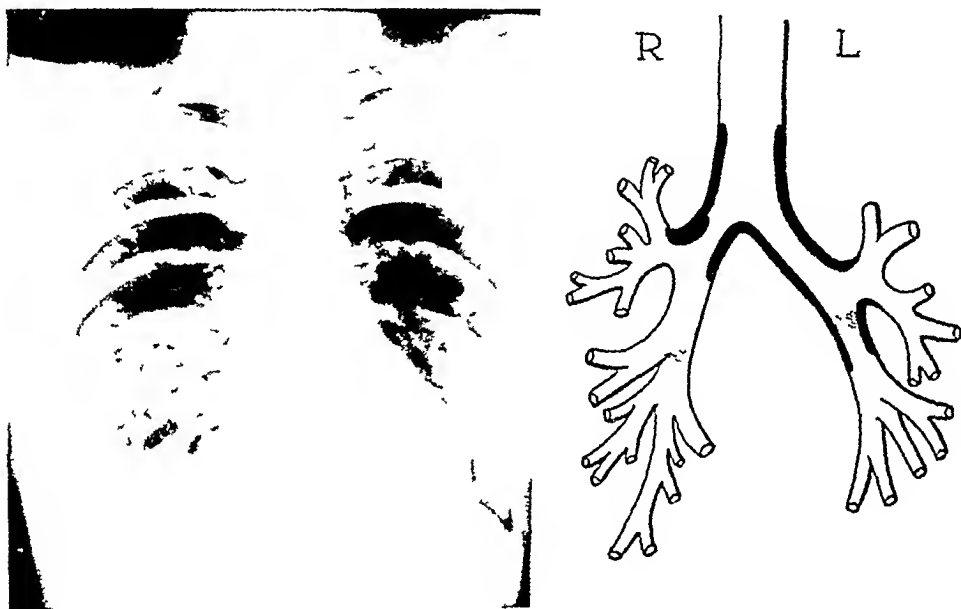
FIG 5 (case 2) (Right) The bronchial tree. Area marked with heavy black ink indicates distribution of tuberculous tracheobronchial lesion visualized at bronchoscopic examination.

with considerable narrowing of the orifice of the right main bronchus. Subsequent progress was not favorable and because of fever, increasing dyspnea and wheezing, she was sent to the clinic for treatment.

On arrival on September 10, 1946, she was hospitalized. Respirations were markedly obstructed and she was obviously ill. Acid-fast bacilli were demonstrated on direct smear of sputum. The sedimentation rate was 51 mm in one hour (Westergren). Roentgenograms of the chest revealed a minimal degree of tuberculosis in the apex of the left lung and at the level of the left first interspace anteriorly (figure 6). On bronchoscopic examination an extensive ulcerating process was found in the lower part of the trachea. The ulceration extended into the left main, left upper, and left lower lobe bronchi (figure 7). The ulcers were covered with granulations and a tenacious gray mucus. There was an inflammatory stricture of the right main bronchus which reduced the orifice to a diameter of 5 mm. The mucosa near the carina was studded with nodules which grossly appeared to be tubercles.

Considerable granulation tissue and secretion were removed and raw bleeding surfaces were left. The patient was able to breathe much better at the conclusion of the examination.

Treatment with streptomycin was instituted on September 12, 1946, and continued for seventy-six days. Streptomycin, 1.5 Gm. in divided doses, was administered by intramuscular injection daily. One-half gram dissolved in 10 cc. of saline solution was nebulized and given each day by inhalation. Daily examinations of sputum were carried out. Nearly all specimens were positive for tubercle bacilli for the first month of treatment. After that it became difficult to demonstrate tubercle bacilli by concentration methods. In the last three weeks of her treatment at the clinic, a few bacilli were demonstrated microscopically on two occasions. The erythrocyte sedimentation rate dropped to 15 mm. in one hour.



Figs 6-7

FIG 6 (case 3) (Left) October 5, 1946. Minimal tuberculosis in apex of left lung and anteriorly at level of the left first intercostal space.

FIG 7 (case 3) (Right) The bronchial tree. Areas marked with heavy black ink indicate distribution of tuberculous tracheobronchial lesions visualized at bronchoscopic examination.

Rather severe symptoms of vestibular dysfunction developed after one month of treatment with streptomycin and it was necessary to discontinue treatment for one week. Parenteral therapy with 1.5 Gm. of streptomycin daily was then resumed but no further drug was given by inhalation.

Bronchoscopic examination, performed two weeks after streptomycin therapy was begun, revealed striking improvement. The ulcers had disappeared from the trachea and were less marked in the left main and lower lobe bronchi. Continued improvement was observed at subsequent bronchoscopic examinations and at the final examination on November 13, 1946, there was no residual ulceration and the mucosa was entirely clean. There was some contraction of the lower part of the trachea but the stenosis of the right main bronchus was less marked and the bronchoscope could be passed into the right lower lobe bronchus.

The patient returned to the sanatorium seventy-eight days after registering at the

clinic Frequent reports concerning her progress had been obtained Cultures of sputum and of gastric contents have been carried out repeatedly but none have been positive for tubercle bacilli Bronchoscopic examinations performed at intervals have revealed that her improvement has been maintained, although she has some cicatricial contraction of the lower part of the trachea and the right main bronchus There has been no evidence to suggest recurrence of tuberculosis during the one and one-half years since the bronchial lesions appeared to have healed

#### COMMENT

The 3 cases reported demonstrate the prompt and apparently permanent healing of ulcerative tuberculosis of the trachea and bronchi which would never have been anticipated with any previous method of treatment There has been no recurrence of disease in these patients during the interval of one and one-half to three years of observation since healing was achieved<sup>2</sup> These cases were unique in that the parenchymal pulmonary tuberculosis in each was relatively minor as compared with the extensive and serious tracheobronchial lesions It is obvious that antibacterial therapy could have no effect on fibrotic stenosis of the trachea and bronchi Yet, when the ulcerating mucosal lesions healed in these cases, there was much less stenosis than was anticipated, and pulmonary resection which had been considered was unnecessary

Equally dramatic results have been observed in 3 additional cases Two of these patients had had thoracoplasty previously for extensive parenchymal disease but bronchial ulceration had persisted and probably had progressed Prompt healing of the bronchial ulceration was observed after treatment with streptomycin but considerable fibrotic stenosis persisted Cultures of the sputum and of gastric contents obtained during fasting were converted from "positive" to "negative" in both cases The third patient responded favorably to treatment for tuberculous disease involving the mucosa of the left main bronchus with extensive ulceration and narrowing but eventually required left pneumonectomy

The use of streptomycin has apparently reduced the danger of bronchoscopic manipulation and biopsy in the presence of tuberculosis We no longer hesitate to remove granulation tissue from the trachea or bronchi, take specimens for biopsy, or dilate stenotic bronchi of tuberculous patients In fact, the removal of obstructing tissue is often apparently essential to the complete treatment of such lesions

The present trend in streptomycin therapy for tuberculosis is toward reduction in dosage Our present practice in the treatment of tracheobronchial tuberculosis is to administer 10 Gm of streptomycin daily in two equally divided doses at twelve hour intervals or at a single injection Even smaller doses may prove to be adequate It has been demonstrated clearly that the parenteral method of administration is far more effective than the aerosol method alone in the treatment of these lesions (3) There is some evidence to indicate that combined

<sup>2</sup> Since this paper was prepared for publication, the 3 patients whose cases are reported herein have been observed further All of them have remained well and there has been no recurrence of the tracheobronchial lesions

therapy may be more rapidly effective than injection therapy only. If aerosol therapy is to be used, it is recommended that 0.5 to 1.0 Gm. of streptomycin be given daily in a concentration of 100 mg. per cc. of physiologic salt solution.

The same toxic reactions which have been observed in most patients treated with streptomycin for any period of time were observed in this group of patients who had tracheobronchial lesions. Vestibular complications were frequent and were troublesome in some of the early cases but should be much less in future cases in which smaller doses of streptomycin will be used.

The excellent results obtained in cases of tracheobronchial tuberculosis have gone a long way toward establishing the efficacy of streptomycin in the treatment of tuberculosis. The introduction of streptomycin therapy has changed the attitude of the medical profession toward tuberculosis of the tracheobronchial tree. What was previously regarded as a most serious complication is now shown to be amenable to therapy. Early and accurate diagnosis of tracheobronchial tuberculosis becomes of great importance now that an effective therapeutic procedure is available.

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# TOXICITY OF STREPTOMYCIN FOR THE AUDITORY AND VESTIBULAR MECHANISMS<sup>1 2, 3</sup>

EDMUND P FOWLER, JR , AND CARL R FEIND

(Received for publication June 16, 1948)

When streptomycin is administered in high dosage, if poorly excreted, or if it is given over long periods of time, toxic reactions become an important consideration. Dysfunction of the vestibular mechanisms is the toxic reaction most frequently encountered. The patient complains of difficulty in walking under certain conditions, vertigo on sudden turning of the head, and trouble focusing his eyes, et cetera. Careful Hallpike (1) caloric measurements using 30° C water for forty minutes or the Gloging mattress test (2) will often bring out dysfunctions which are not superficially apparent.

Reports from the Veterans Administration on 900 patients who received 18 to 20 Gm of streptomycin per day state that 80 per cent of the patients had vertigo (3) by the fourth week of treatment. Although subjective vertigo usually disappeared, hypofunction or abolition of the vestibular response persisted. On one gram of streptomycin per day, vestibular disturbances developed in approximately 30 per cent of the patients by the sixtieth day of treatment.

At high dosage levels, auditory involvement is not infrequent and tends to follow vestibular loss if therapy is continued. On the other hand, it seems to improve if administration of the drug is discontinued before the damage is complete. We have seen 2 cases recover almost all of their hearing after having experienced quite a severe hearing loss. Incidentally, there is also some return of vestibular function in a few cases where the dosage was discontinued before total vestibular loss occurred. Auditory involvement in the lower dosage levels has very rarely been encountered.

Up to and including the present, most dosage reports and recommendations of dosages for therapy have been in grams of streptomycin per day. The same dosage is often given to both the small emaciated female weighing 38 Kg and the average male of 70 Kg, or the large obese patient of 100 Kg. It will be shown later in this paper that the most important factors in the production of toxic symptoms in animals is the blood level of streptomycin and the length of time this blood level is maintained. Tompsett has made similar observations in humans (4). The larger the dose the shorter the period before otic dysfunctions occur, so dosage should always be prescribed in mg per Kg of body weight per day.

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<sup>2</sup> Presented before the Medical Section, as part of the Symposium on *Chemotherapeutics and Antibiotics*, at the 44th Annual Meeting of the National Tuberculosis Association, New York, New York, June 16, 1948

<sup>3</sup> This study was aided by grant from the Division of Research Grants and Fellowships of the National Institute of Health, U S Public Health Service

Another important consideration in streptomycin therapy is the excretory powers of the kidney. Many observers have reported the rapid onset of severe otic dysfunction in patients with high concentrations of drug in the blood as a result of faulty renal excretion. Unexpected otic symptoms could be avoided or minimized by an adequate intermittent check of renal function.

When there is damage to the vestibular system from any cause, the body tries to compensate with the optic and proprioceptive mechanisms. The damage from streptomycin is no exception. More or less compensation is readily achieved by children and most young adults, but is a more serious problem in the older age groups. All groups encounter difficulties in locomotion in the dark or over rough terrain though they may show no disability in bed or on smooth well-lighted hospital floors. So-called "cerebellar exercises" seem to increase the speed of compensation. Putting the patients into classes where several individuals are successfully overcoming their handicap is bound to have an effect on those who cling to their vertigo for various psychological reasons.

The questions which come to all of our minds are where and what is the mechanism of the lesion of streptomycin poisoning and how is it produced. Extensive histological study of the labyrinth, the CNS tracts, and their nuclei have failed to show any definite or consistent lesion which was not also found in control animals. Theoretically the lesion would appear to be located in the vestibular ganglion (Scarpa's) or in the brain stem, but convincing localization of pathology is yet to be demonstrated.

Streptomycin seems to act like an allergen. Some humans and animals do not develop toxic manifestations on the same dosage that affects others. Streptomycin produces hives, rashes, angioneurotic edema or eosinophilia in certain individuals. All of these suggest an allergic type of reaction. Is it possible to combat the toxic effects of streptomycin with antihistamine or, as suggested by Romansky (5), is it possible to prevent the effects by a desensitization regimen? Experiments attempting to answer these questions were carried out in the following manner.

Cats had been found to follow very closely the clinical symptoms displayed by humans so they were selected for the study. All animals during the experiment were tested for vestibular function by rotation, using an electric motor-driven turntable. They were rotated ten times in ten seconds. The postrotational nystagmus was observed visually and timed. When 60 r.p.m. no longer elicited a response, they were rotated at 120 r.p.m. for twenty turns and, when this no longer elicited a nystagmus, the vestibular mechanism was considered defunct. Moving pictures of the eyes were made on a good cross-section of animals at various stages of loss. These rotational experiments seemed even more accurate for the determination of quantitative vestibular losses than the Hallpike calorics used in humans. Hawkins has made similar determinations (7). Rotation experiments are more difficult to perform on patients, however.

Gross auditory tests were made using a sharp short noise at 60, 80, 100, and 110 decibels. The noise apparatus was screened from the view of the cats. The auditory response was observed through conditioned palpebral reflexes. When

the response could not be elicited with 110 decibels, the animals were considered deaf

All animals were given streptomycin<sup>4</sup> by the subcutaneous route in two divided doses a day. Figure 1 is a graph plotting streptomycin dose per kilogram of body weight per day versus days of therapy. (The outside scale is the equivalent dose in grams per day in a 60 Kg man.) The first heavy line represents the day of lesion in 14 control cats on various streptomycin dosage regimens. Above 400 mg per Kg per day the animals died in a very few days in severe dehydration. From this lethal level to one of 66 mg per Kg per day (a therapeutic dose) there was a gradual prolongation of the onset of otic dysfunction.

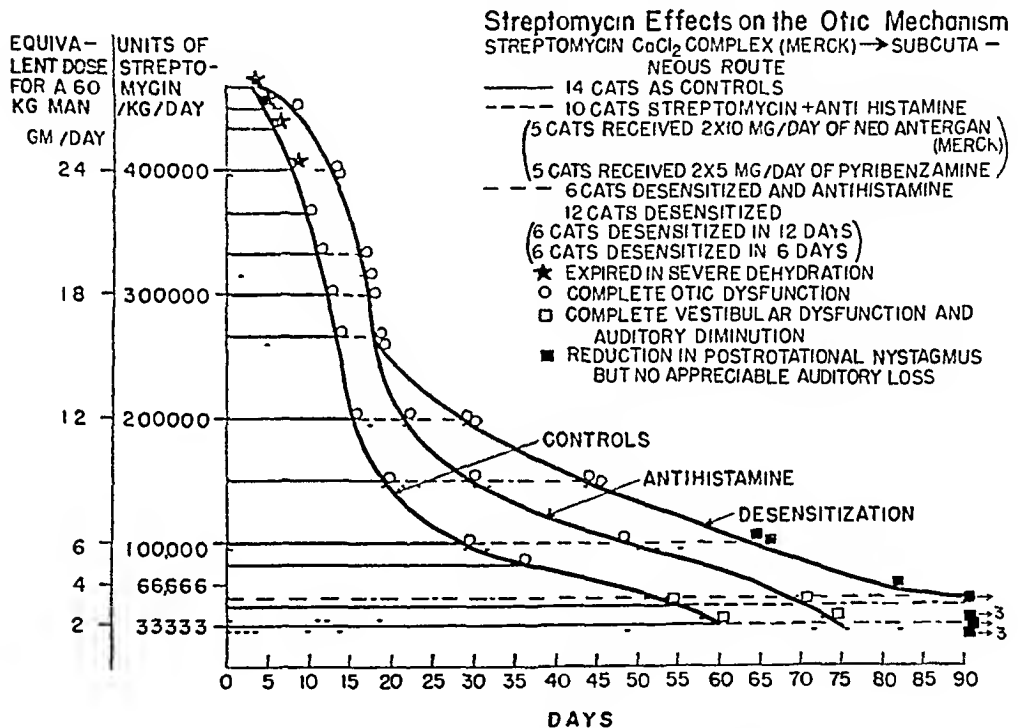


FIG 1 Streptomycin effects on the otic mechanism

The points represented by an "O" are the days of complete otic dysfunction. At the lower therapeutic level the points represented by a square are the days of complete vestibular dysfunction but only diminution of auditory function.

The second heavy line represents the day of vestibular loss in 10 animals receiving streptomycin plus antihistamine. Five cats received 20 mg per day of Neo-antergan. Five cats received 10 mg per day of pyribenzamine. The approximate 5, 10, and 15 day extension of the day of complete vestibular dysfunction as compared to the control group may be seen. The addition of antihistamine brought on dehydration sooner and in a more severe form than

<sup>4</sup>The streptomycin used in these experiments was the calcium chloride trihydrochloride complex kindly supplied by Merck and Co., Rahway, New Jersey.



streptomycin alone and the animals in general showed greater signs of discomfort, however the time before the otic symptoms developed was prolonged. The last line, which is superimposed on the second line as far as the 250 mg level, represents the day of complete vestibular dysfunction of 12 cats that were given a desensitization regimen. Briefly, this was done by starting them on a very small dose of streptomycin and bringing them up fairly rapidly to both toxic and therapeutic levels. The desensitization was accomplished in six days at the lower levels and twelve days at the higher more toxic levels. Notice that in high levels there seems to be no protection. An analogous lack of protection is demonstrated by desensitized ragweed sufferers when they are exposed to excessive amounts of the allergen.

All of the desensitized animals ate well, kept themselves clean, and showed no signs of dehydration until the day of practically complete vestibular dysfunction, in spite of the fact that they were receiving doses which made non-desensitized animals in nearby cages very ill. This well-being of the desensitized animals is not understood but may be of prime importance. The combination of desensitization and antihistamine in 6 cats did not produce a superior protection as they also fall in this last line. Of equal interest, besides the prolongation of the onset of symptoms, is the fact that the cats under a desensitization regimen at a therapeutic level (which is equivalent to a human 2 gm per day dosage) did not after more than 100 days of therapy show any auditory loss. They showed only a slight diminution of response to rotation and no vestibular symptoms.

The toxic effect in cats as well as humans (4) occurs more or less regularly with a certain total dosage except with very low levels. For example, the control series curve approximates a total dosage of 3 Gm per Kg of body weight, the antihistamine curve approximates a total dose of 5 Gm per Kg of body weight, and the last line, the desensitization regimen, approximates a total dose of 6.5 Gm in the intermediate level. That the cats on a desensitization regimen tolerated more than twice the dose of the control animals before they had a complete vestibular loss is statistically significant. It is hard to explain just why streptomycin seems to be less toxic in desensitized animals. Whether it is true desensitization or an acquired tolerance is not known, but it is believed that any information about the toxicity of the drug is useful. At the present time we feel justified in at least recommending antihistamine along with streptomycin therapy. The two chief objections to a desensitization regimen are (1) that in acute cases one would not have the time to carry out the desensitization, and (2) that in the desensitization period one might give the microorganism involved time to become resistant or one might be allowing resistant strains of bacteria to develop without affecting the nonresistant one soon enough.

If experiments show that bacterial resistance to the drug does not develop in the short desensitization period, then cases of long term therapy for tuberculosis would be greatly aided. The distressing symptoms of vertigo, nausea, and anorexia certainly interfere with the attainment of the rest, good nourishment, and peace of mind required for the successful care of tuberculosis.

Our experience with many tests and several hospitals leads us to recommend the following regimen for the evaluation of otic dysfunction in streptomycin-treated patients

(1) One audiogram in a quiet room before the drug is started. Another audiogram done after one week of therapy and further audiograms should be done after treatment has terminated or if auditory symptoms develop during treatment. Any hospital where large numbers of hearing tests are being done should have an audiometer and a sound-proof booth for testing. The latter can now be obtained, prefabricated, for around \$1,000 and a satisfactory one can be built by the hospital carpenter for about \$300.00.

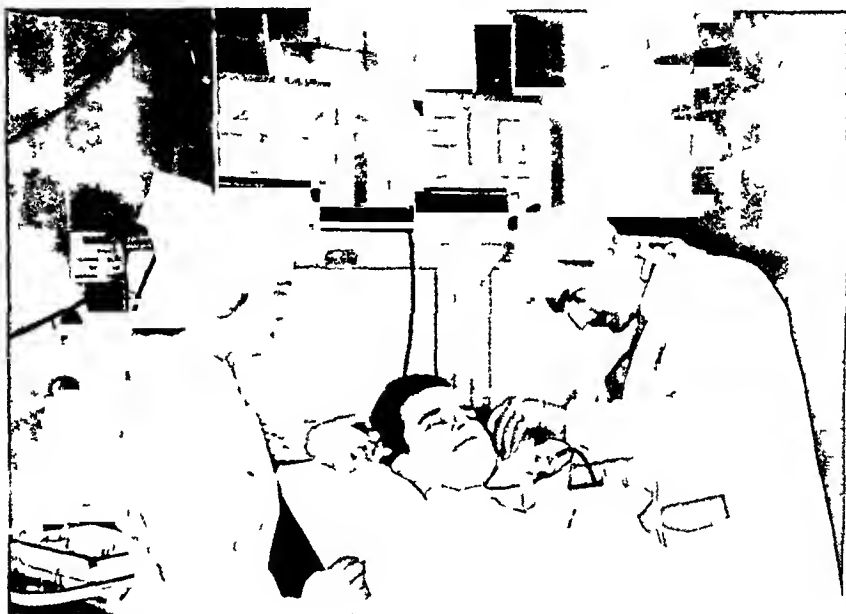


FIG. 2 The horizontal canals are upright with the patient lying  $30^\circ$  from the horizontal. When the temperature is checked with a thermometer at the meatus, much more accurate tests are obtained.

(2) Caloric tests should be done before therapy begins, when and if the symptoms develop, and after treatment is terminated.

a. The best caloric test is the Hallpike test (1) using  $30^\circ\text{C}$  and  $44^\circ\text{C}$  water, controlled by a water bath with a thermostat and stirrer (figure 2).

b. If the Hallpike test cannot be done, a Kobrak test using 5 cc of ice water with the head back  $60^\circ$  from the vertical is useful. If 5 cc produces no response, the instillation should be continued up to 50 cc.

(3) If there is any indication of vestibular loss by the above tests, the patient should be given exercises in balance, walking along a line, standing on one foot, looking from right to left, turning gently, throwing bean bags about, walking up and down stairs, walking on rough ground, et cetera. A good test of general function is the Glomg mattress test, which consists of walking on a firm mattress first without, then, if possible, with a blindfold (2).

Finally we should like to remind you that it is an ill wind that blows no one any good. Elsewhere one of us (6) has reported the use of toxic effects of streptomycin on the vestibular mechanism in the alleviation of the vertigo in Meniere's disease.

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# REPEATED TRANSCUTANEOUS AUTOLYTIC TUBERCULIN TESTS IN CHILDREN<sup>1</sup>

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## INTRODUCTION

In 1913 (1) it was pointed out and demonstrated by experiment that tubercle bacilli liberate tuberculin (tuberculo-protein) by autolysis. Tuberculin containing a biologically active tuberculo-protein was described originally by Koch as 'Old Tuberculin' in the nineties and was obtained by him from a bouillon filtrate after the massive culture of mammalian tubercle bacilli.

The tuberculo-protein was isolated first chemically in crystallizable and precipitable form from the filtrate from a nonprotein simple synthetic medium by Long and Seibert in 1928 (2). The latter preparation, as PPD, was used for accurate intracutaneous test purposes and as a standard tuberculin. Though chemically pure, it did not prove suitable, however, for transcutaneous testing.

The autolytic tuberculin, containing about 10 per cent undenatured biologically active tuberculo-protein and prepared from bacilli free of extraneous materials and chemically unaltered, as well as bacteriologically uncontaminated, possessed properties advantageous to preservation in pure form as well as suited to the preparation of a satisfactory transcutaneous test material (3, 4, 5, 6). It could be suspended in dry form in a suitable inert nonirritating nonwatery liquid containing a cellulose preparation, so the autolytic tuberculin would adhere satisfactorily upon application to the skin. As a result of its hygroscopic nature, it would dissolve by absorbing moisture in close approximation to the skin to permit the immediate action of the tuberculin for the tuberculin allergic hypersensitive test for tuberculosis. The reaction to this test is self-limited by nature and causes no remote focal or systemic reactions, as may occur with intracutaneous or other injection tests for the tuberculin (hypersensitive) reaction, and therefore can be used without reservation even in the tuberculous.

Because of the applicability of this test to repeated use and its simplicity of administration, the question arose whether the test could cause hypersensitivity to itself when repeatedly applied, since it has been claimed by some that an Arthus phenomenon (hypersensitive allergic condition) can develop to large repeated injections of tuberculin. The writers have been unable to verify this, especially when using bacteriologically uncontaminated and pure tuberculo-protein or autolytic tuberculin in as large amounts as possible for the sensitizing agent. Tuberculin has been used so extensively both experimentally and clinically that errors in results have been numerous and deductions at times have

<sup>1</sup> From the Research Department, National Jewish Hospital, Denver, Colorado

lacked critical evaluation. This is well pointed out by an article in 1946 (7) in which it was noted that

Tuberculin testing for diagnostic case finding surveys has proved itself reliable by intracutaneous (Mantoux—with proper amount of tuberculin) and transeutaneous techniques (Corper). An interpretation of the significance of reactors and the relation to nonspecificity are presented. The fallacy of evaluating tuberculin tests on the basis of high numbers of reactors is expounded. For case finding surveys, the test which elicits the minimum number of reactors among persons without tuberculous disease is the superior test. A set of criteria based on efficacy as well as reliability is recommended for acceptable tuberculin testing programs.

It is obvious that no materials should be in the test reagent which can produce or elicit a reaction in themselves or can cause evident nonspecific irritation when applied, particularly to the skin of the tuberculous or any normal individual. In order to note whether such reactions can be caused by the adhesive (the cellulose preparation) or the solvent used for applying the autolytic tuberculin for test purposes, the vehicle containing all the ingredients except the autolytic tuberculin powder was applied to the skin of over 100 tuberculous patients (in all states of the disease) at the National Jewish Hospital at Denver and to the skin of over 50 normal individuals. In each case, at least two applications were made in various places on the arms and back. The applications were allowed to remain adherent to the skin until they naturally separated and dropped off, which in over 75 per cent of the cases required from three to six days or more, while the remainder adhered to the skin over two days when properly applied. In no case was there any evidence of either mechanical or chemical irritation, and there was no evidence of maceration of the skin from accumulation of moisture under the application. Even individuals with a sensitive skin tolerated the applications well and without irritation of any kind.

In previous tests on the tuberculous, it was determined that a period of contact of several hours would suffice to produce a positive tuberculin reaction with the autolytic tuberculin "plastotest". As a rule, however, the test reagent should remain in contact with the skin for one to two days after application for best results. The speed of development of the intracutaneous autolytic tuberculin test reaction is about the same as that following intracutaneous tests with specific amounts of pure tuberculin.

#### OBSERVATIONS

In order to determine whether the transeutaneous autolytic tuberculin "plastotest" (Corper) could cause the development of tuberculin hypersensitiveness, a total of 223 children and adolescents in an orphanage, ranging in ages from 5 to 20 years of age, were tested repeatedly. For the first month, tests were made at weekly intervals and then each month for six months from the initiation of the first test. In all cases, at least two tests were applied either on the forearms, the upper arms, shoulders, or backs, and in many cases four applications of "plastotest" to different sites were made.

In all the 223 children, the period of study covered the six months interval and note was made of any conditions such as other infections, sunburn, et cetera, which might in any way vitiate a reliable test. In many cases a chest roentgenogram was taken for correlation purposes to note particularly whether any evidence existed of parenchymal tuberculous involvement, enlargement of lymph nodes at hilum, Ghon tubercles or significant calcifications of any kind. In obtaining the roentgenograms, stress was laid particularly on the definitely positive reactors. It is intended to continue testing at the nine month and twelve month intervals after initiation of the tests in all available cases.

The results of the tests are summarized in table 1 in order to note the number of the total 223 children tested who never disclosed a positive reaction to the repeated duplicate (or more) applications of the transcutaneous autolytic tuberculin "plastotest." In table 2, the positive reactors are given more detailed evaluation mainly to note what effect repeated testing would produce on the

TABLE 1

*The Results of Repeated Transcutaneous Autolytic Tuberculin "Plastotests" over a Period of Six Months on 223 Orphanage Children*

TOTAL CHILDREN TESTED	SEX	TOTAL PERSISTENTLY NEGATIVE	TOTAL DEFINITELY POSITIVE	TOTAL BORDERLINE POSITIVES
223	Males—151 (45 + 81 + 25)*	108	23	23
	Females—69 (30 + 35 + 4)*	54	6	9

\* The numerals in parentheses indicate the number of children in each age group starting with the first numeral, from 6 to 10 years, the second, 11 to 15, and the third, 16 to 20 years.

tuberculin hypersensitiveness of the definitely positive, slightly positive, or questionable cases.

It is noted from the results recorded in table 1 that at least 162 of 223 children repeatedly tested with the transcutaneous autolytic tuberculin "plastotest" consistently gave negative reactions to the test. According to sex, 108 of a total of 151 males and 54 females of a total of 69 remained negative throughout the test period. This represents more than 70 per cent of the total, and 70 per cent of the males, and 78 per cent of the females, who were consistently negative reactors. These figures would appear to justify the conclusion that repeated duplicate applications of the transcutaneous autolytic tuberculin test for prolonged periods does not tend to produce a hypersensitive condition to tuberculin in the recipients of the test.

Whether or not the application of the transcutaneous autolytic tuberculin test is capable of altering consistently the reaction obtained in the positive or slightly positive tuberculin hypersensitive case is disclosed in an examination of the findings obtained in the positive cases and recorded in table 2.

The results recorded in table 2 summarize the serial findings in the positive

TABLE 2  
The Variations in the Transcutaneous Reactions to the Autolytic Tuberculin "Plastotest" Applied Repeatedly to Positive or Slightly Positive Tuberculin Reactors over a Period of Six Months

TOTAL NUMBER OF CASES (POSITIVES)	SEX TOTAL (POSITIVES)	DETAILED FINDINGS	
		Definite positive reactors	Slightly positive or questionable reactors
61	Males 46	23	23
		6 to 10 years	6 to 10 years
		12-3-4 to 9*	1 to 578-6†
		2 to 5-69-178	468-1 to 357
		67-3580-124	18-2 to 7
		123-4 to 9	
		11 to 15 years	11 to 15 years
		23468-157	14 to 8-23
		234-15 to 8-67	256-13,478
		8-2 to 7-1	345-126 to 8
	Females 15	6 to 10 years	6 to 10 years
		467-358-12	35 to 8-124
		1 to 8	2 to 578-16
		16 to 20 years	1 to 8
		16-78-2 to 5	3 to 8-12
		1 to 8	146 to 8-235
		6 to 10 years	6 to 10 years
		1 to 5-6 to 9	79-1 to 68
		123-4-5 to 8	5579-1 to 18
		17 to 9-1236-5	5 to 8-1 to 4
		11 to 15 years	11 to 15 years
		1 to 47-568	1358-2467
		8-346-1257	3 to 68-127
		8-0-1 to 7	13 to 5-26 to 8
		3 to 8-12	3 to 8-12
		2356-1178	2356-1178
		3167-1258	3167-1258

\* The first numeral before the dash indicates the order number of the tests when a positive reaction was obtained, 13 indicating on the first and third test period or 1 to 3 on the first, second, and third tests, while the second numeral following the first dash indicates a slight or questionable positive reaction. When appearing, the third numeral following the second dash were the order of a negative reaction or questionable positive reaction.

† The markings or numerals in this group give only two sets of numerals, the first being the order of the series when a slightly or questionable positive reaction occurred and the second, following the dash, indicating the order of occurrence of a negative test. In all cases either 8 or 0 test periods were performed, the numeral 8 or 0 indicating this





test readings Frequent repeat tests assume importance also in this light, since errors thus are minimized to the advantage of the reliability of any tuberculin test Duplicate tests, which can be performed easily also with the transcutaneous autolytic tuberculin test to assure better observation as well as proper application, yield more reliable results in the individual case and possess definite advantages

#### SUMMARY AND CONCLUSIONS

Frequent and repeated application, in duplicate or more, of the transcutaneous autolytic tuberculin "plastotest" (Corper) extending over more than a six month period does not produce a hypersensitiveness to tuberculin or to the transcutaneous test in children between the ages of 5 to 20 years Neither does the repeated application of the transcutaneous tuberculin test accentuate or suppress an already existing hyper sensitiveness to tuberculin in children

#### SUMARIO

##### *Repetidas Transcutirreacciones Autolíticas a la Tuberculina en los Niños*

La frecuente y repetida aplicación, por duplicado o más, de la "plastorreacción" transcutánea autolítica a la tuberculina (Corper) durante un período de más de seis meses no produce hipersensibilidad a la tuberculina o a la transcutirreacción en niños de 5 a 20 años de edad Tampoco acentúa o suprime la repetida aplicación de la transcutirreacción con tuberculina, una hipersensibilidad preexistente a la tuberculina en los niños

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# A SLIDE CULTURE METHOD FOR THE EARLY DETECTION AND OBSERVATION OF GROWTH OF THE TUBERCLE BACILLUS<sup>1 2, 3</sup>

A Preliminary Report

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## INTRODUCTION

The characteristic slow growth of *Mycobacterium tuberculosis* imposes a severe handicap on those engaged in clinical or research work in the field of tuberculosis. This is especially true in the clinical study of tuberculosis because the symptoms, signs, roentgenographic changes, and laboratory findings other than the bacteriologic, are not sufficiently distinctive to be absolutely pathognomonic of the disease. It has been frequently noted that a diagnosis of tuberculosis in the absence of bacteriologic proof is often questionable. In order that the diagnosis be certain, the tubercle bacillus must be demonstrated. The problem is becoming more acute because of the widespread use of the various roentgenographic techniques employed to discover tuberculosis in apparently healthy individuals (1). As a result of these surveys, the proportion of minimal disease coming under observation is increasing (2, 3, 4, 5) and, therefore, the number of patients in whom it is impossible to demonstrate the tubercle bacillus by smear or concentrate is also increasing. Failure to make the proper diagnosis in suspicious cases frequently leads either to the exposure of a nontuberculous individual to the environment of a sanatorium or to a delay in the proper treatment. Such a delay not uncommonly results in progression of the disease (5).

Microscopic examination of a direct smear of material harboring tubercle bacilli is obviously the simplest and most economical method by which the micro-organism may be demonstrated. Unfortunately this method is very indelicate, since it has been estimated that it requires 100,000 tubercle bacilli per cc of smeared fluid in order that the organism may be detected in this manner (6). The fact that there is frequently an insufficient number of organisms in biological fluids for demonstration by direct examination is so well known that it is hardly deserving of comment. It may be useful, however, to cite the figures of Pinner (7) who found that in 533 cases from which the tubercle bacillus was recovered, approximately 60 per cent were "positive" on direct smear or sputum concentrate, 16 per cent more were "positive" on culture of the sputum, 5 per cent were "positive" on direct examination of the gastric concentrate, and 18

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per cent were "positive" only on culture of the gastric contents. These figures are derived from the study of patients in all stages of tuberculosis and adequately demonstrate that direct examinations of sputum smears or concentrates are only about 60 per cent efficient. The inefficiency of the microscopic examination of the sputum is further emphasized by the findings of Decker, Ordway and Medlar (8) who have shown that, in persons with minimal tuberculosis, the tubercle bacillus can be demonstrated by direct examination of the smear in only about 6 per cent. In 269 cases of minimal tuberculosis reported by them, smears were "positive" in 5.9 per cent, whereas culture or guinea pig inoculations demonstrated the presence of tubercle bacilli in 69 per cent of these cases. These figures agree with those reported by other workers (9).

Although it is not within the scope of this paper to enter into the controversy as to which procedure, culture or guinea pig inoculation, is the most useful in detection of the presence of the tubercle bacillus, it should be pointed out that, in spite of the many articles in the literature which advocate the use of culture methods alone (10, 11, 12, 13), from the evidence now available it would seem that when accuracy is the only consideration both methods should be used in each case being studied (14, 15, 16).

The time required for growth to become apparent appears to depend somewhat upon the procedures used and to a greater extent upon the number of organisms in the inoculum. In the ordinary laboratory practice the interval between inoculation and the macroscopic appearance of growth is from 3 to 8 weeks. Exceptionally, colonies first appear as early as 5 days and as late as 3 months following inoculation.

In order to decrease the interval between inoculation and detection of growth, smears have been made of the material scraped from the surface of the culture media at intervals during the period of cultivation. In this manner the time necessary to demonstrate the acid-fast organisms can be considerably shortened. Johnston (17) showed that microscopic examination of the material scraped from the surface of his diagnostic cultures disclosed the presence of the tubercle bacillus in an average time of 20 days, whereas macroscopic growth appeared only after 41.3 days. In this way, 21.3 days were gained. While there is no doubt that the diagnosis can be made more quickly in this manner, it is not practical because of the high rate of contamination (17).

In 1945, a new medium was described by Dubos (18), which was reported by him to produce rapid growth of the tubercle bacillus. Although this medium was designed for purposes other than primary isolation of the tubercle bacillus from pathological materials, it has been used for that purpose by several workers with encouraging results. Foley (19, 20) has reported the successful use of Dubos media for the cultivation of tubercle bacilli from various biological fluids. Goldie has also reported good results with Dubos media in the isolation of tubercle bacilli from sputum (21). Foley noted growth in an average time of 10.6 days, and Goldie reports positive cultures in 8 to 14 days.

Dubos and Middlebrook (22) have recently described a modification of the original Dubos medium, making it more suitable for the primary isolation of

tubercle bacilli In this paper they state "Suffice it to say that fairly rapid growth of tubercle bacilli (7 to 15 days) has often been obtained in the liquid media with sputa, spinal fluid, and pleural exudates which have failed to reveal tubercle bacilli on direct microscopic examination "

Sattler and Youmans (23) have been unable to demonstrate any increase in the rate of growth of the tubercle bacillus in Dubos media

The final evaluation of Dubos medium cannot be made at this time but, even if the most favorable reports are confirmed, there will still remain a relatively long interval between the time the specimen is sent to the laboratory and the time the report is received

Although it appears that progress has been made in increasing the rate of growth by alteration of the culture medium, the fact remains that the tubercle bacillus grows slowly For this reason it seemed that it might be profitable to approach this problem by other means, namely the microscopic detection of early growth

Robert Koch (24), in his paper of 1882 in which he described the tubercle bacillus, also described the preparation of cultures designed for direct microscopic observation of the growth He accomplished this by coagulating blood serum on watch glasses or in "small hollow glass blocks" in such a way that it remained transparent In this manner he was able to demonstrate growth of the tubercle bacillus by the end of the first week by means of magnification of 30 to 40 diameters

Since Koch's report of what may be termed the micro-culture method, we are aware of no further work in the use of this method for the primary isolation of tubercle bacilli until 1941, although others used such a technique as a research tool, utilizing as inocula organisms from pure cultures (25, 26) In 1941, Pryce (27) described a method in principle very similar to that of Koch, although he was apparently unaware of Koch's work Pryce demonstrated that it was possible to treat a sputum film on glass with acid, thus destroying organisms other than the tubercle bacillus He advocated preparing the sputum on the floors of Petri dishes or in slide cells made by putting glass rings over the treated smear, he used whole blood as the medium With this method growth was evident microscopically in from one to six days

In 1943 Rosenberg (28) attempted to use Pryce's methods but abandoned them He found the contamination rate excessively high when Petri dishes were used, the slide cell method he found too laborious for large scale use He devised a method of slide culture in which the smears, prepared on half slides and treated with acid, were placed in water filled bottles with perforated screw caps The water was removed with a needle attached to a suction pump and replaced with Kirchner's serum-salt mixture Microscopic growth was visible within a week This method, although ingenious, is obviously too complicated for general use

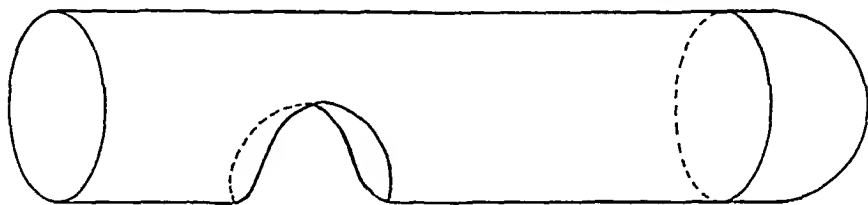
Finally, others have described micro-culture techniques for research purposes These methods are not adaptable to any large scale application (29, 30)

Thus there was ample evidence that growth of the tubercle bacillus could be

detected microscopically within a week. It appeared, however, that as yet there had been no method of micro-culture devised which did not have serious disadvantages or was not needlessly complicated.

#### METHOD

From a specimen of sputum<sup>4</sup> six smears are prepared on new glass slides of the usual size (75 by 25 mm) which are suitable for labeling. The smears differ in no way from those ordinarily used for microscopic examination, except that they are somewhat thicker. The smears are allowed to dry and are then put in a glass rack which in turn is placed in a covered stain dish (commercially obtainable) and submerged in 6 per cent sulphuric acid for 20 minutes (31). After this interval, in order to remove the acid, the rack containing the slides is transferred with aseptic technique successively to three similar dishes filled with sterile water. The slides remain in each of these dishes 10 minutes. They are then placed in the tubes containing the medium (one slide per tube) and incubated at 37°C. On the second, fourth, and sixth days, two cultures are taken out, the slides



#### CULTURE TUBE

FIG 1 Culture tube. See text for description. (Drawn by W. A. McGilvray.)

are removed from the tubes, allowed to dry, fixed with heat, labeled, stained, and examined under the microscope. Early in this work half the smears and cultures were stained with auramine. This staining method was abandoned because it was of less value than the Ziehl-Neelsen technique.

Special tubes<sup>5</sup> (figure 1) have been designed specifically for this purpose in such a way that they can be laid horizontally in the incubator. The tubes measure 180 mm in length, with an inside diameter of 35 mm. One hundred and ten mm from the closed end of the tube is an indentation 20 mm in depth, the purpose of which is to prevent the medium from reaching the cotton plug when the tube is horizontal. During incubation a piece of ordinary laboratory glass tubing is placed in the indentation to keep the tubes from rolling. In the horizontal position the maximum opportunity for oxygen diffusion is provided, since the entire sputum film is only slightly beneath the surface of the medium, and, in addition, a large surface of liquid is exposed to air. The amount of medium necessary (20 cc) is indicated by a mark on the tube.

The medium used for the cultures reported in this paper consisted of 50 per cent Kirchner's solution of electrolytes, glycerol and asparagin (32), and 50 per cent whole citrated blood. In a series now being done, the use of this mixture has been abandoned and Kirchner's basic medium with serum albumin<sup>6</sup> added in a concentration of 0.5 per cent.

<sup>4</sup> The specimens of sputum have not been digested or concentrated.

<sup>5</sup> Available through Technical Equipment Corporation, Denver, Colorado.

<sup>6</sup> Bovine plasma fraction V, Armour Laboratories, is satisfactory.

(33) has been used. The growth obtained with the albumin medium appears to be as good as that with the blood, and the fact that the Kirchner albumin mixture is a clear solution is a distinct advantage, since the slides need not be washed upon removal from the tubes before they are dried and fixed. Whether this is the ideal medium for this purpose remains to be determined and studies on this problem are in progress in this laboratory.

Cotton plugs for the tubes are not sterilized in the culture tubes because of the inhibitory effect of distillates from the cotton on the growth of the tubercle bacillus (34). The plugs are placed in glass cylinders of the same diameter (35 mm) as the tubes and sterilized in the autoclave. At the time the medium is placed in the tubes, the plugs are transferred to them.

### RESULTS

All the sputa cultured were from patients whose specimens had at least on one occasion been positive. Two smears were made from each single specimen to be cultured and these were carefully searched for tubercle bacilli.

A total of 140 cultures were made. Twenty-five cultures were made from specimens of sputum which contained numerous bacilli, 39 from specimens containing few bacilli, 40 from specimens which contained rare organisms, and 36 from those in which only 3 or fewer organisms were found in the entire search. The specimens of this last group would probably have been called negative by the standards ordinarily used, since no organisms were seen until the time of searching had been prolonged to one hour or more. This classification of sputa as to whether they contain numerous, few, or rare organisms was made in accordance with that recommended by the Committee on Standard Laboratory Procedure of the American Trudeau Society (35).

Of the total number of cultures upon which this study is based, 37.1 per cent, or 52 cultures, were contaminated. If this high rate of contamination could not be reduced, obviously the method would be of little value. However, many of the factors contributing to the excessive contamination rate have been eliminated by trial and error as work with this new method has progressed. It was necessary, for example, to determine the length of time the smears should remain in acid in order to destroy contaminating organisms. Early in this work, the time was varied from 10 to 45 minutes, but later it was standardized at 20 minutes, since this period proved to be satisfactory. Longer periods of time did not seem to inhibit growth of the tubercle bacillus, but shorter periods appeared to be inadequate. Since all of the cultures are included in the study, the early cultures kept in acid for the shorter lengths of time contributed to the high rate of contamination reported for the series.

The use of the glass rack mentioned above for transferring the slides from one container to another was begun during the course of the work because it was felt that the possibility of air contamination would be less than when the slides were transferred individually. Again, the results of the earlier method are included.

Perhaps the most important factor in the high contamination rate is the fact that during most of the work reported in this paper it was necessary to share a laboratory where a great deal of other work was being done, including animal

autopsies When a clean workroom became available, the contamination rate dropped markedly

Following these various improvements, the rate of contamination in about 100 cultures of a series to be reported later is approximately 1.5 per cent

Of uncontaminated cultures (88), growth was present in 89.8 per cent This figure is without regard to the length of time the culture was incubated, that is, 2, 4, and 6 day cultures are included

TABLE 1

*Summary of Results (Uncontaminated Cultures) with Slide Culture Method for Detection of M. tuberculosis*

Over-all percentage of cultures showing growth is shown and in addition the results in relation to the time of incubation (uncontaminated cultures)

	NUMBER	GROWTH PRESENT		GROWTH ABSENT	
		Number	Per cent	Number	Per cent
Total	88	79	89.8	9	10.2
2 days	29	26	89.7	3	10.3
4 days	34	28	82.4	6	17.6
6 days	25	25	100	0	0

TABLE 2

*Slide Culture Method for Detection of M. tuberculosis*

The number of organisms seen on direct smear of the specimen is correlated with growth after two, four and six days' incubation (uncontaminated cultures)

TIME INCUBATED	ORGANISMS SEEN IN DIRECT SMEAR							
	Numerous		Few		Rare		3 or less	
	Growth	No growth	Growth	No growth	Growth	No growth	Growth	No growth
days								
2	3	0	4	2*	9	1	10	0
4	5	0	7	0	6	3*	10	3†
6	4	0	7	0	8	0	6	0

\* These were the cultures stained with auramine (see text)

† In two of these faulty staining technique may account for the failure

In table 1 may be seen the results with uncontaminated cultures separated into 2, 4, and 6 day groups Growth was present in 89.7 per cent of 2 day cultures, in 82.4 per cent of 4 day cultures, and in 100 per cent of those incubated for 6 days The fact that growth was detectable in such a high percentage of 2 day cultures indicates that routine examination at that time is far from unproductive

Table 2 shows results in relation to the number of organisms seen on examination of the direct smears of the sputum specimens

Of the 9 (10.2 per cent) cultures which failed to show growth in spite of being uncontaminated, 2 were stained with a faulty technique, 5 were stained with auramine, and in each instance cultures from the same specimen incubated the

same length of time and stained with carbolfuchsin showed growth, the remaining two were 2 and 4 day cultures. In 20 of the contaminated cultures, growth of tubercle bacilli was present.

The appearance of the colonies of *M. tuberculosis* growing in the slide cultures may be seen in figures 2 through 7.

#### DISCUSSION

Although it has been known since 1882 that growth of the tubercle bacillus could be detected after one week's incubation by means of the low power lenses of the microscope and attempts have been made to utilize this fact, apparently none of the methods thus far devised is sufficiently practicable for routine use.

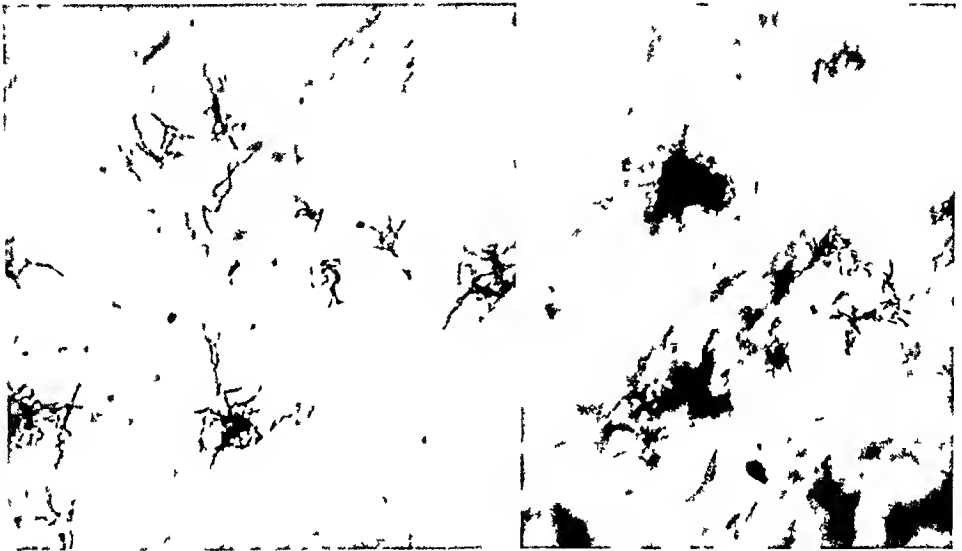


FIG 2 (Left) Two day culture ( $6 \times 90$ ), Ziehl-Neelsen stain  
Small colonies are visible on the background of the sputum film

FIG 3 (Right) Three day culture ( $6 \times 90$ ), Ziehl-Neelsen stain  
This illustrates the marked beading of the organisms which is occasionally seen

The present method is reported because it is believed to be sufficiently simple for general use by laboratory technicians. All the equipment required is inexpensive and commonly used in laboratories, with the exception of the tubes which can now be obtained through a commercial supply house. The technique is not complicated and it is believed that it may be feasible to simplify it even further. For instance, it is possible that the time the slides remain in water can be shortened. We have perhaps been overcautious in our effort to be certain that the acid was completely removed.

Because of the characteristic morphology of the colonies they are easily identified. After six days' incubation they are readily visible with the low power of the microscope ( $6 \times 10$ ). The low power is also usually adequate for the examination of the 4 day culture. Occasionally, however, it is necessary to use greater magnification ( $6 \times 45$ ). It is necessary to use the high dry lens to examine



the 2 day culture, and not uncommonly the oil immersion lens is required (6 x 90). On some occasions cultures have been examined after 24 hours' incubation and

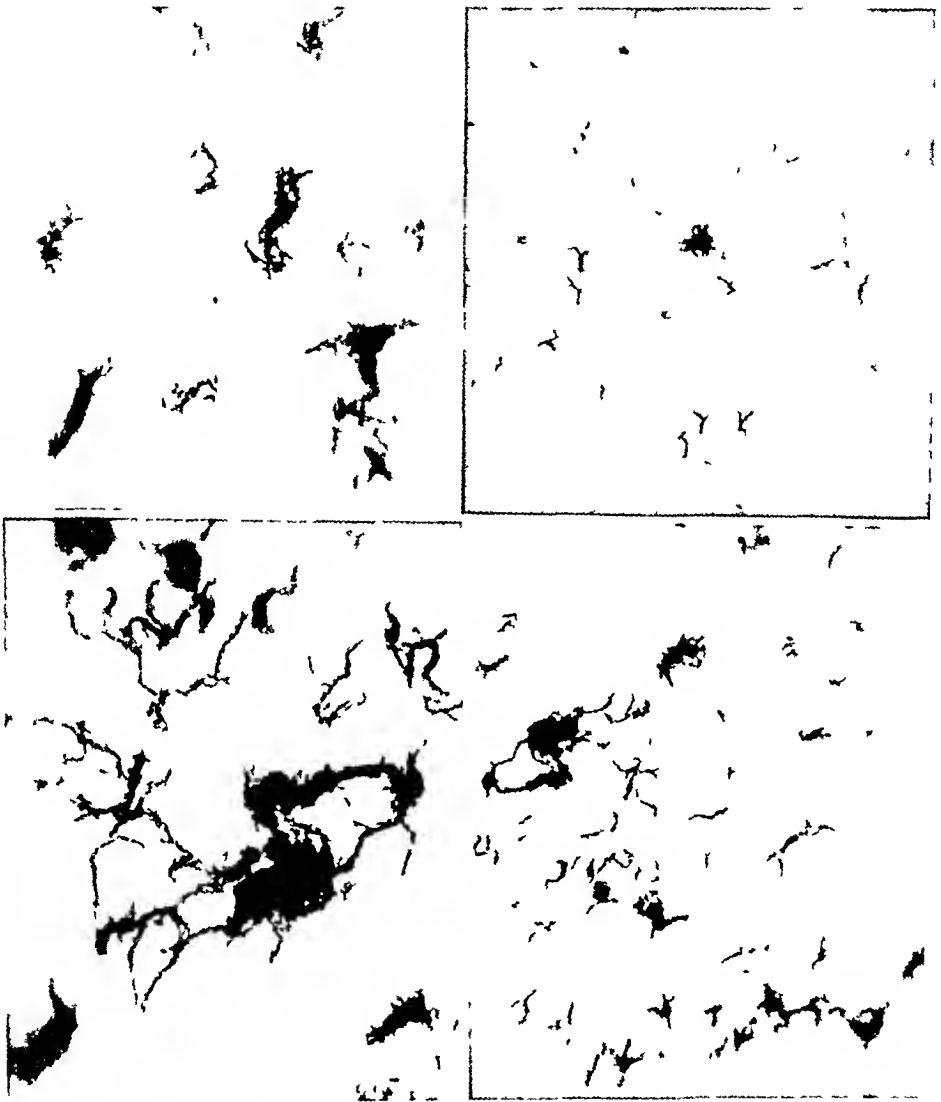


FIG 4 (Upper left) Four day culture (6 x 90), Ziehl-Neelsen stain  
No sputum is visible in this field

FIG 5 (Upper right) Four day culture (6 x 45), Ziehl-Neelsen stain  
This illustrates how easily colonies of this age are seen with low magnification

FIG 6 (Lower left) Six day culture (6 x 90), Ziehl-Neelsen stain without counterstain

FIG 7 (Lower right) Six day culture (6 x 45), Ziehl-Neelsen stain without counterstain

growth has been apparent. One quickly becomes proficient in the study of slide cultures, but it is advisable at the start of work with this method to culture a strongly "positive" sputum in order to become familiar with the appearance of the colonies (figures 2 through 7).

We are testing the diagnostic efficiency of the slide culture method in another laboratory by comparing its accuracy with that of a conventional culture method. Work is also being done in this institution in an effort to adapt the technique to the determination of streptomycin sensitivity of the tubercle bacillus directly from the sputum, without preliminary isolation.

With this technique, further information about the morphology and growth patterns of the acid-fast bacilli may be obtained and comparisons between various pathogens and between pathogenic and nonpathogenic organisms made. The development of colonies can be closely followed by serial termination of growth at short intervals. This method will also provide more precise information as to the effects on growth produced by alterations of media.

#### SUMMARY

A technically simple method by which *M. tuberculosis* can be cultivated directly from sputum on slides is described. Growth of the microorganism is evident in from one to six days.

Although the experience is too limited to justify final conclusions, the results suggest that this may be a useful method for the rapid diagnostic demonstration of the tubercle bacillus. It is believed that, because of its simplicity, this method will be a useful research tool.

#### SUMARIO

*Técnica del Cultivo en Placas para el Descubrimiento Temprano y Observación del Crecimiento del Bacilo Tuberculoso. Comunicación Preliminar*

El método, técnicamente sencillo, aquí descrito, permite cultivar el *M. tuberculosis* directamente del esputo, en placas. Las colonias son visibles en uno a diez días.

Si bien las observaciones son demasiado limitadas para justificar conclusiones definitivas, los resultados indican que esta técnica puede ser útil para el rápido hallazgo del bacilo tuberculoso, con fines de diagnóstico. Parece que, debido a su sencillez, también va a resultar útil para investigación.

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# THE PHARMACOLOGIC AND CHEMOTHERAPEUTIC ACTION OF SOME NEW SULFONES AND STREPTOMYCIN IN EXPERIMENTAL TUBERCULOSIS<sup>1, 2</sup>

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## INTRODUCTION

In 1940 Rust and associates showed that 4,4'-diaminodiphenylsulfone (DDS) had a favorable effect in experimental tuberculosis in rabbits infected with an avian strain (1). Later the same was shown to be true for experimental tuberculosis in guinea pigs infected with a human strain (2). Since then many attempts have been made to develop compounds chemically related to or derivatives of DDS with the objectives of decreasing toxicity and increasing activity. The first objective has been realized, for there are now many derivatives of DDS that are less toxic than the parent compound. The second objective has not met with as much success.

Shortly after the discovery of streptomycin, it was shown that the use of this antibiotic, together with suitable sulfones, resulted in mutual potentiation of action so that the combined effect in experimental tuberculosis was greater than the sum of effects from the two drugs when used alone (3). Hence the further need of sulfones of low toxicity, if only of moderate activity, as supplementary aids in the treatment of tuberculosis with streptomycin.

Generally speaking there are two types of derivatives of DDS. (1) The disubstituted derivatives, in which a hydrogen in each of the two amino groups is replaced by a substituent, *e g*, Promin, Diasone and the more recent Sulphetrone (4), and (2) the monosubstituted derivatives in which one of the amino groups remains free. In the latter class, the alkyl monosubstituted derivatives have been found to be the least toxic and most effective (5). These compounds, however, are characterized by low absorbability. Further experimentation showed that the introduction of a hydroxyl group into the alkyl substituent increased absorbability without sacrifice with respect to toxicity and activity.

The present paper is a report on the actions of the newer disubstituted derivative Sulphetrone (4)<sup>4</sup> and the monosubstituted 4-amino-4'- $\beta$ -hydroxyethylaminodiphenylsulfone (6)<sup>5</sup> synthesized in this laboratory and hereafter designated

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<sup>4</sup> 4,4'-Bis ( $\gamma$ -phenyl-*n*-propylamino) diphenylsulfone-tetrasodium sulfonate. Supplied by Dr. Edwin J. de Beer, the Wellcome Research Laboratories.

<sup>5</sup> 4-Amino-4'- $\beta$ -hydroxyethylaminodiphenyl sulfone crystallizes as dimorphic forms melting at 130.5-131.5°C and 143.5-144.5°C. The two forms have shown about the same absorption, toxicity and chemotherapeutic activity, the latter tested in experimental pneumococcus infection in mice. We are indebted to Dr. Augustus Gibson and Dr. Max Tishler of Merck & Company for the supply of a large quantity of the compound.

hydroxyethyl For comparison, data are also included on the older and better known disubstituted derivative Promin and the parent substance DDS Promin and Sulphetrone are water soluble and can be administered parenterally, DDS and hydroxyethyl are only slightly soluble in water and are usually administered orally

#### EXPERIMENTAL

Table 1 shows the structural formulas of these compounds and their DDS equivalent Hydroxyethyl on direct diazotization at room temperature, according to the Bratton and Marshall technique, represents 46 per cent of DDS, close to the theoretical value Promin and Sulphetrone are 15 and 13 per cent, respectively, showing their instability, for theoretically, having no free amino group, they should have no diazotization value Both of these compounds in 0.25 *N* hydrochloric acid containing some trichloroacetic acid are decomposed at 100°C, the diazotization values being short of the theoretical values, probably because of the presence of impurities Under similar conditions, there is no splitting of the molecule of hydroxyethyl This was demonstrated by keeping a solution of 0.3 Gm. of hydroxyethyl in 0.25 *N* hydrochloric acid containing 2.5 per cent trichloroacetic acid at 100°C under a reflux condenser for one hour Concentration and neutralization of the solution by sodium hydroxide yielded 0.3 Gm. of pure hydroxyethyl, identified by its melting point and a mixed melting point determination with the authentic compound

Figure 1 illustrates the values obtained on direct diazotization of DDS and Promin at room temperature and after acid hydrolysis, as described in a previous report (7) Plotting light absorption obtained with a Fisher electrophotometer against concentration in mg. per 15 cc., curve 1 represents values obtained for DDS The direct values and those obtained after heating were identical Curve 2 represents the values obtained for Promin on direct diazotization and curve 3 after acid hydrolysis When the blood or urine of an animal receiving DDS is analyzed by the two procedures, the values are identical, as expected if the DDS is unaltered in the animal body When the blood or urine of an animal receiving Promin by oral administration is analyzed in the same manner, the values are also identical which suggests that Promin is metabolized in the body to DDS Sulphetrone gives similar results The properties of a metabolite isolated from the urine of man receiving the hydroxyethyl indicate that this is not degraded to DDS This metabolite was obtained, by a method to be described later, in solid condition melting at 170 to 174°C and showing diazotization and coupling with the Bratton-Marshall reagents A mixture of this material with authentic DDS crystals of m.p. 176 to 177°C melted at 142 to 145°C, which shows that the metabolite is not DDS Although the quantity of material available was insufficient for complete purification and identification, the possibility of the oxidation of hydroxyethyl in the human body to the previously described glycine derivative (6) is mentioned<sup>6</sup>

<sup>6</sup> Using a similar technique of isolation DDS was recovered nearly quantitatively and identified by melting point when added to normal urine In like manner DDS was also



*Toxicity studies* Data in table 2 give the approximate  $LD_{50}$  in rats on oral administration as 1.0 Gm per Kg for DDS, 3 to 4 Gm per Kg for Promin and more than 4 Gm per Kg for Sulphetrone and hydroxyethyl. On intravenous injection the  $LD_{50}$  for Promin is between 3 and 3.5 Gm per Kg, for Sulphetrone 4.5 Gm per Kg. In terms of DDS equivalent, the toxicity of the two disub-

## DIAZOTIZATION CURVES

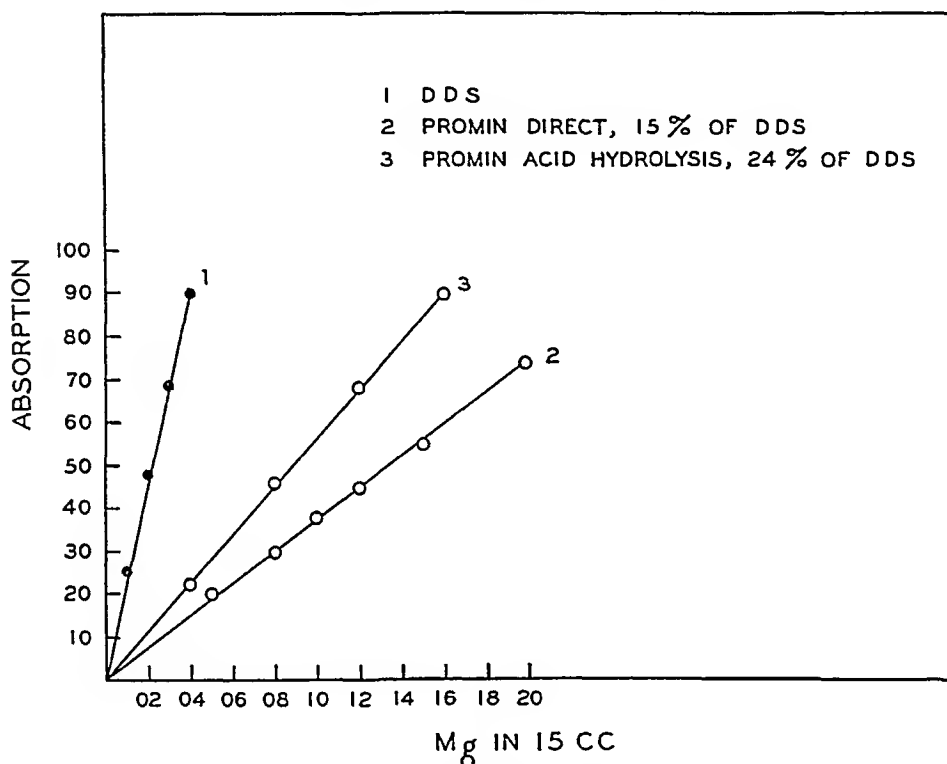
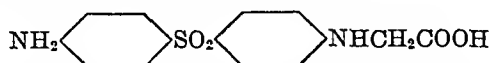


FIG 1 Diazotization curves of DDS and Promin on direct diazotization and after acid hydrolysis at  $100^{\circ}\text{C}$  for one hour. Values for DDS are identical, two sets of values are obtainable with Promin. Similar analysis of blood and urine of animals receiving Promin orally yield nearly identical values as with DDS suggesting the degradation of Promin to DDS.

stituted derivatives is almost identical and considerably greater than that of hydroxyethyl.

recovered from urine of rabbits receiving DDS and identified by melting point. Moreover a substance with m.p.  $199$  to  $200^{\circ}\text{C}$  was isolated from the urine of a cat receiving hydroxyethyl and when mixed with the pure glycine derivative



it gave a m.p. of  $201$  to  $202^{\circ}\text{C}$ . The pure glycine derivative melts at  $202$  to  $203^{\circ}\text{C}$ . This isolated material also gave a diazotization curve identical with that of the glycine derivative. These experiments will be described in detail in a later publication.



The chronic toxicity in rats when fed in a semisynthetic diet is shown in table 3. The tolerated concentration of DDS is 0.2 per cent of the diet. At this concentration the blood levels were 1.2 to 2.6 mg per 100 cc. Promin is tolerated at a concentration of 0.8 per cent, almost exactly the same as DDS when computed on the basis of DDS content. Sulphetrone under the same conditions

TABLE 2

*Acute Toxicity of 4,4'-diaminodiphenylsulfone (DDS) and Derivatives in Rats Weighing 125 to 175 Gm*

DOSE  Gm/Kg	ROUTE	MORTALITY, NUMBER DIED/NUMBER USED			
		DDS	Promin	Sulphetrone	Hydroxyethyl
0.8	Oral	3/10			
1.0	Oral	6/10			
3.0	Oral		4/10		
4.0	Oral		6/9	2/10	0/10
3.0	I V		3/10	0/10	
3.5	I V		7/10		
4.0	I V		5/5	2/10	
4.5	I V			7/15	

TABLE 3

*Chronic Toxicity of 4,4'-diaminodiphenylsulfone (DDS) and Derivatives in Young White Rats Weighing 60 to 80 Gm when Fed in the Diet in the Concentrations as Indicated*  
Mortality in relation to number used (M) and blood levels mg per 100 cc (BL) at the end of the experimental period

PER CENT DRUG IN DIET	DDS			PROMIN			SULPHETRONE		
	M	Days	BL Mg per 100 cc	M	Days	BL Mg per 100 cc	M	Days	BL Mg per 100 cc.
0.2	0/10	50	1.2-2.6						
0.3	10/10	2 to 11							
0.5	10/10	4 to 10							
0.8				0/10	46	9-26			
1.0	10/10	1 to 6		4/10	11 to 38				
1.5				8/10	3 to 38	6.4-22.0			
3.0				10/10	3 to 43		0/9	105	10.8-34.0
5.0							2/10	46*	12-33

\* Subnormal growth

is much less toxic for it is tolerated in concentrations of 3 to 5 per cent. The blood levels at the high concentration of Sulphetrone in the diet were not significantly higher, however, than those of Promin at the concentration of only 0.8 per cent in the diet, suggesting that the relatively low toxicity of Sulphetrone may be due to lower absorability.

The same appears to be true from the data on cumulative toxicity in guinea

pigs, shown in figure 2 Three groups of 10 guinea pigs each were fed by stomach tube 10 Gm per Kg twice daily of Promin, Sulphetrone and hydroxyethyl, respectively All the animals in the Promin group were dead after 10 doses Only one of the 10 in the Sulphetrone group died after 14 doses and 2 in the hydroxyethyl group after 20 doses All the others survived 30 doses However, blood level determinations made at comparable periods after the administration

### CUMULATIVE TOXICITY IN GUINEA PIGS 10 Gm/Kg TWICE DAILY MORTALITY CURVES

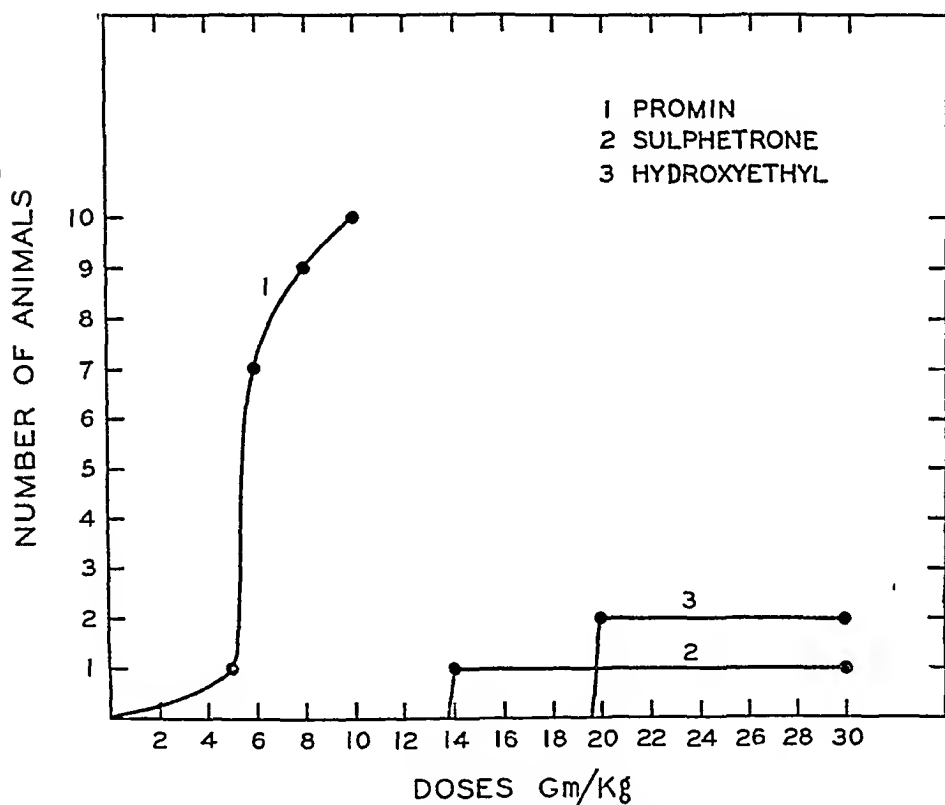


Fig 2 Cumulative toxicity of Promin, Sulphetrone and 4-amino-4'- $\beta$ -hydroxyethyl-aminodiphenylsulfone in guinea pigs One Gm per Kg twice daily orally

of the respective compounds indicated much higher values for Promin than Sulphetrone or hydroxyethyl The average blood levels in the Promin group were 26 to 48 mg per 100 cc, Sulphetrone 5 to 10 mg per 100 cc and the hydroxyethyl group 1 to 7 mg per 100 cc

Hemoglobin determinations showed a reduction on an average of from 14.3 to 12.0 Gm per 100 cc during treatment for the Promin group, from 14.8 to 12.5 Gm per 100 cc for the Sulphetrone group and from 14.9 to 13.3 Gm per 100 cc for the hydroxyethyl group

In table 4, data of the chronic toxicity of some of these compounds in cats are

given The compounds were administered daily, incorporated in a ration of 100 to 200 Gm ground lean beef, for voluntary consumption Two animals in the first group received 50 mg per Kg DDS, the second group of 2 animals received the DDS equivalent as Promin, the third group of 2 animals received first the DDS equivalent as Sulphetrone followed by twice the DDS equivalent and the last 3 animals in the fourth group were given from 1 to 4 times the DDS equivalent as the hydroxyethyl compound The DDS animals lost weight

TABLE 4  
*Chronic Toxicity and Effect on Blood Pigments in Cats*  
*Oral Administration*

COMPOUND	NUMBER	WEIGHT KG		DOSES	TOTAL DOSE	BLOOD LEVELS	BLOOD PIGMENTS, GM PER 100 CC			
		Initial	Final				Total Hb	HbO <sub>2</sub>	MHb	SHb
DDS	1	4.2	2.3	30 × 50*	1.5	mg per 100 cc				
	2	3.5	1.7	65 × 50	3.25					
Promin	3	3.2	2.7	70 × 200	14.0	16.0	12.1	10.0	0.9	1.5
	4	3.4	1.5	70 × 200*	14.0	19.5	11.7	8.9	1.1	2.1
Sulphetrone	5	2.9	3.2	68 × 200 16 × 400	20.0	14.0	12.6	9.7	1.0	2.5
	6	2.9	3.5	68 × 200 16 × 400	20.0	11.6	15.5	13.2	0.9	1.9
Hydroxyethyl	7	3.2	2.7	34 × 100 14 × 400	9.0	3.0	12.6	11.9	0.8	1.2
	8	3.9	3.7	5 × 100 29 × 200 16 × 400	12.7	3.5	13.0	11.4	0.7	1.1
	9	3.7	3.2	5 × 100 29 × 200 13 × 400	11.5	2.4	13.3	13.2	0.5	0.5
Controls, average of 9 determinations in 5 normal cats							14.3	13.9	0.3	0.4

\* Died

rapidly, developed anorexia, frequently refusing to consume their ration, and thus failed to ingest the drug One of the animals died after 30 doses The Promin animals tolerated treatment somewhat better but on the whole displayed similar effects and one died after 70 doses The Sulphetrone and hydroxyethyl animals accepted the drugs well, showed no visible effects and appeared in good health Spectrophotometric analysis of blood pigments towards the end of the observation period by the method of Evelyn and Malloy (8) revealed more methemoglobin and sulfhemoglobin in the DDS, Promin, and Sulphetrone animals than in the hydroxyethyl animals The reduction in oxyhemoglobin

in relation to the total hemoglobin was also more pronounced in the first three groups

Blood level determinations made uniformly at about 18 hours after feeding, at the time when the animals were receiving 200 mg per Kg Sulphetrone and 100 to 200 mg hydroxyethyl, indicated much higher drug concentrations in the Promin and Sulphetrone groups than in the hydroxyethyl group

Summing up the data on toxicity it may be concluded that Promin is about as toxic as DDS when dosage is computed on the basis of DDS equivalent, while Sulphetrone and hydroxyethyl are much less toxic. Since the blood levels were

TABLE 5

*Blood Levels in mg per 100 cc in Guinea Pigs at Various Intervals Following the Oral Administration of Three Sulfone Derivatives in Doses of 0.1 to 2.0 Gm per Kg*

HOURS	DOSE	PROMIN	SULPHETRONE	HYDROXYETHYL
	Gm/Kg	Mg per 100 cc	Mg per 100 cc	Mg per 100 cc
1	0.1	2.0	2.1	1.2
3		2.4	2.6	0.8
5		2.7	3.0	0.5
24		1.1	trace	0
1	0.5	3.6	2.4	2.4
3		8.0	4.0	3.2
5		13.0	4.6	2.9
24		2.8	2.6	0.7
1	1.0	7.3	4.3	3.4
3		9.1	5.5	4.0
5		9.0	6.3	5.0
24		13.0	3.6	1.6
1	2.0			6.1
3				7.5
5				4.7
24				2.4

generally lower for the last two compounds the question of absorption, tissue distribution, and excretion was considered next

*Metabolism studies* Data on the absorption of these compounds from the gastrointestinal tract of the guinea pig, as judged by drug concentration in the blood, are given in table 5. Blood level determinations were made at various intervals up to 24 hours following a single dose of 0.1 to 1.0 Gm per Kg of Promin and Sulphetrone and up to 2.0 Gm per Kg hydroxyethyl. The highest blood levels were obtained with Promin, the lowest with hydroxyethyl. In rabbits, given 0.5 Gm per Kg of either Promin or Sulphetrone orally, the Promin blood levels were more than twice as high as the Sulphetrone, as shown in figure 3.

To determine the relative retention of Promin and Sulphetrone, each was

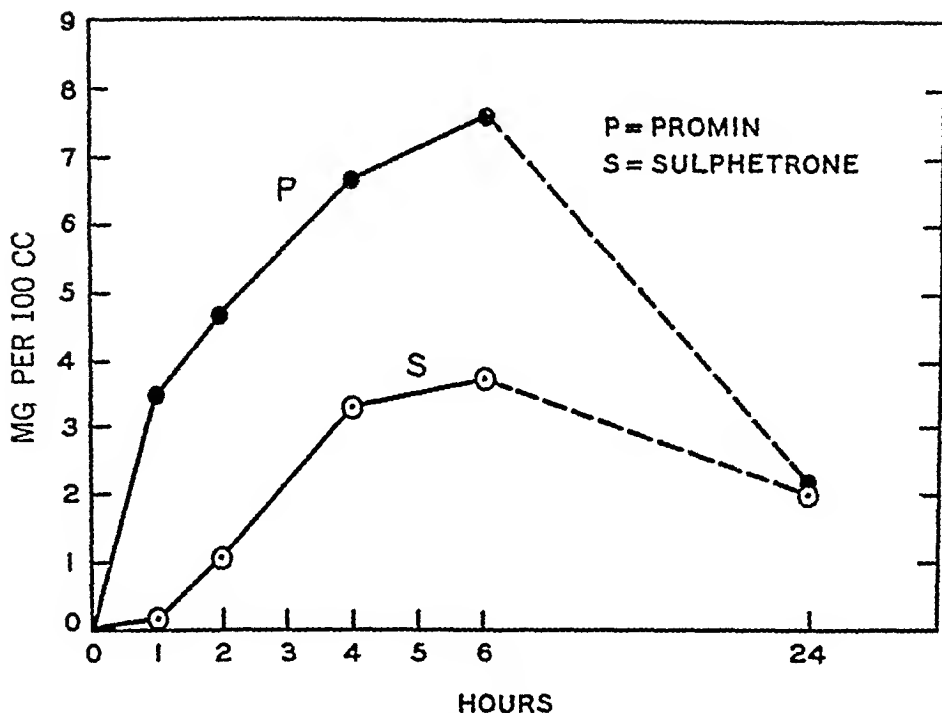


Fig 3 Blood levels following oral administration of Promin and Sulphetrone in rabbits. Significantly higher blood levels of Promin suggest better absorption.

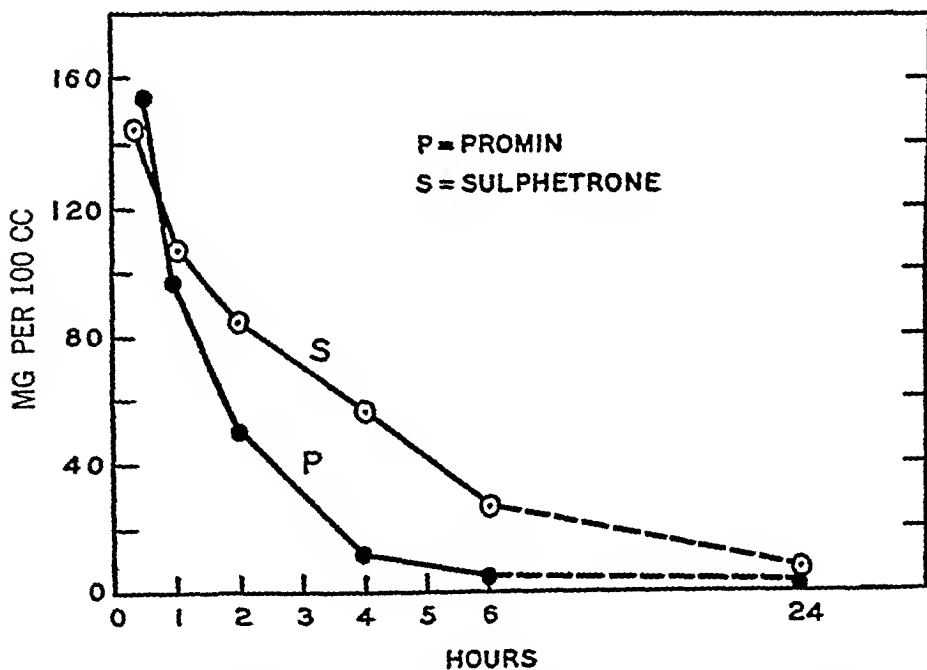


Fig 4 Blood levels following intravenous injection of Promin and Sulphetrone in rabbits. Results indicate better retention of Sulphetrone.

injected intravenously in rabbits in doses of 0.5 Gm per Kg and blood levels determined at stated intervals during 24 hours, with the results as shown in figure 4. It is evident that both drugs leave the blood stream rapidly, though Sulphetrone appears to be retained somewhat better than Promin.

Further data on the metabolic fate of Promin and Sulphetrone are given in figure 5. Both drugs are excreted in the urine to the extent of about 60 per cent of the dose administered when given intravenously. Moreover, the acid hydro-

### URINARY EXCRETION OF PROMIN AND SULPHETRONE IN RABBITS AFTER INTRAVENOUS AND ORAL ADMINISTRATION OF 0.5 GM/KG.

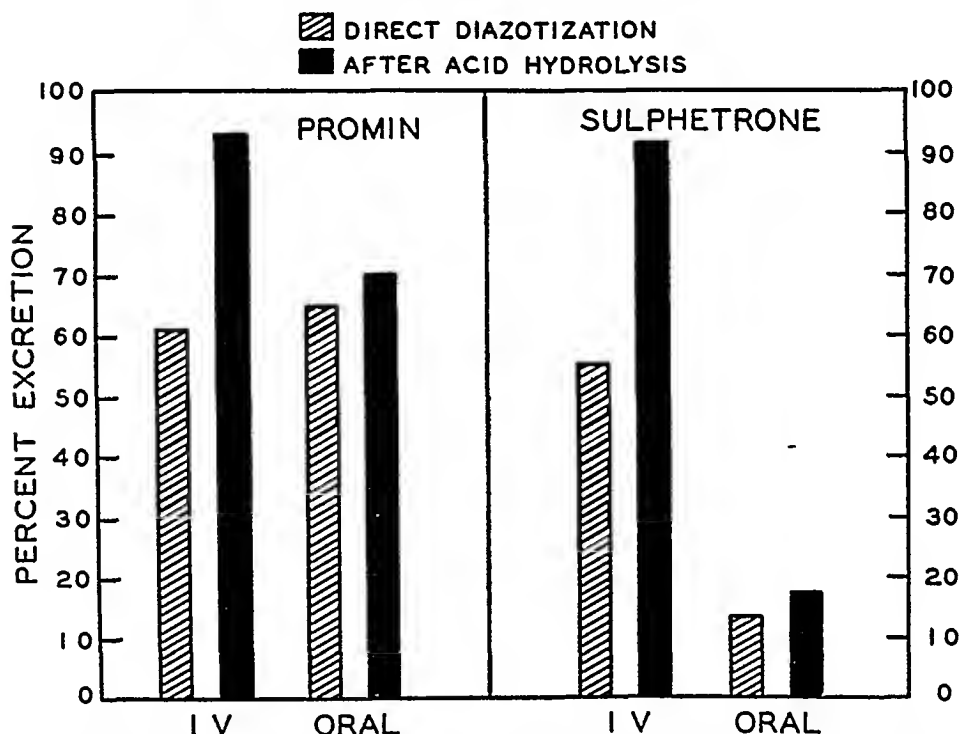


FIG. 5 Urinary excretion of Promin and Sulphetrone on oral and intravenous administration in rabbits in relation to dose administered and metabolic fate. Results indicate degradation of both to DDS on oral administration and poorer absorption of Sulphetrone.

ysis diazotization values are higher for both drugs compared with direct diazotization values. This suggests that both compounds are excreted to a large extent, unchanged, when given intravenously. On oral administration the urinary excretion of Promin is still about 60 to 70 per cent of the dose administered while in the case of Sulphetrone only 15 per cent of the dose given is recoverable in the urine, indicating much poorer absorption. The acid hydrolysis diazotization values on oral administration are nearly identical with the direct diazotization values in both drugs suggesting their degradation to the parent substance.

The urinary elimination of hydroxyethyl in relation to the dose administered was studied in rabbits and in man. The experiments in rabbits are summarized in table 6 and show that, regardless of the dose administered orally, nearly 50 per cent is recoverable from the urine in 24 hours. An experiment in 3 human subjects to whom the compound was administered orally in 2 Gm doses three times during the day (approximately 0.1 Gm per Kg) gave results, shown in table 7, which almost paralleled the results obtained in rabbits. From 40 to 60 per cent of the dose administered was excreted in the urine, and most of it during the first day.<sup>7</sup>

TABLE 6  
*Absorption and Excretion of Hydroxyethyl in Rabbits*

HOURS	BLOOD LEVELS MG PER 100 CC		
	0.1 Gm/Kg	0.5 Gm/Kg	1.0 Gm/Kg
1	1.2	2.3	3.7
2	0.9	1.9	3.7
4	0.9	1.9	4.2
6	0.7	1.5	3.7
24	trace	trace	1.3
Urinary excretion, percentage of dose			
24	45	46	52

TABLE 7  
*Blood Levels and Urinary Excretion of Hydroxyethyl in Man*  
Dose 2 Gm—8 00 a m, 12 00 m and 4 00 p m

SUBJECT	BLOOD LEVELS, MG PER 100 CC, HOURS				URINARY EXCRETION, PER CENT OF DOSE		
	2	4	7	24	First day	Second day	Total
HB	0.4	0.5	0.9	0.6	43	0.9	43.9
AK	0.5	0.6	1.0	0.7	55.8	4.6	60.4
GK	0.7	0.6	0.9	0.6	38.5	1.5	40.0

The low blood levels compared with the relatively high urinary excretion following the oral administration of hydroxyethyl suggested the possibility of a preferential distribution of the compound in the tissues. This was studied in several guinea pigs after a single dose of 0.5 Gm per Kg, and the average results are given in figure 6. The lowest concentrations, estimated as hydroxyethyl, were found in the erythrocytes, the plasma showed somewhat higher concentrations than whole blood, and the liver, kidney, spleen, and lungs gave values ranging from 3 to 10 times those of whole blood. Estimations of the compound

<sup>7</sup> We are indebted to Doctors Howard M. Payne of Freedman's Hospital and Philip Kilbourn of the Tuberculosis Division, Public Health Service, for their cooperation.

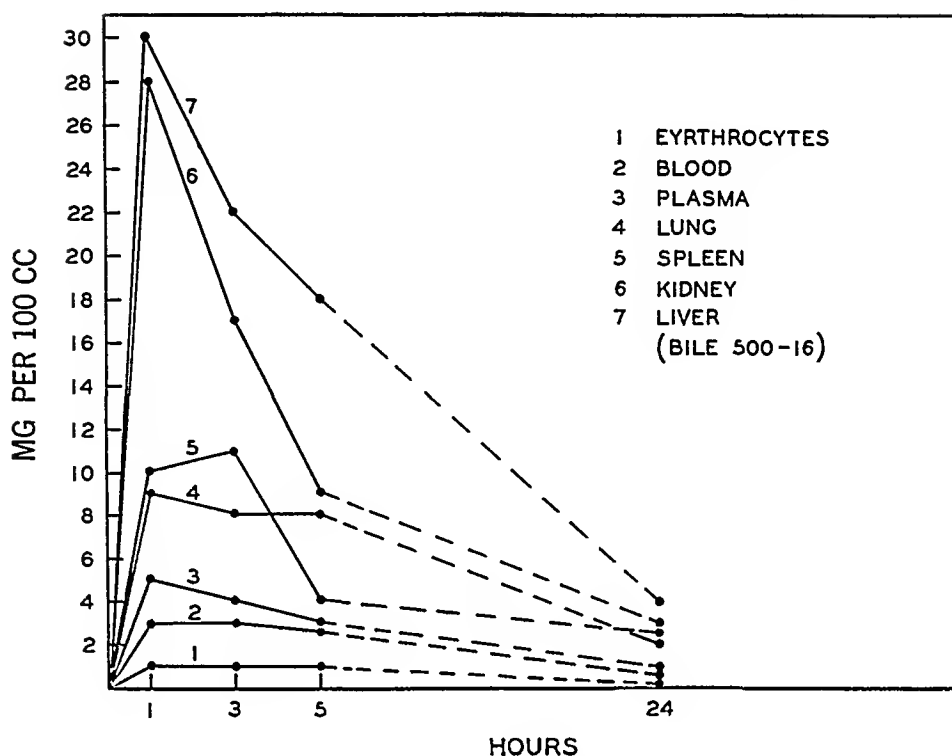


FIG 6 Distribution of 4-amino-4'- $\beta$ -hydroxyethylaminodiphenylsulfone in the tissues of guinea pigs Average of 3 to 4 animals Highest concentration in liver and kidney, lowest in erythrocytes

TABLE 8

*Chemotherapeutic Activity in Experimental Pneumococcus Type I Infection in Mice*

TOTAL DOSE	ROUTE	PER CENT SURVIVAL OF INFECTED MICE	TOXICITY LD <sub>50</sub> IN NORMAL MICE	LD <sub>50</sub> /SD <sub>50</sub>
Hydroxyethyl				
Gm/Kg			Gm/Kg	
4 0	OS	73	>8 0	>8/3
3 0	OS	51		
4 0	SC	75		
3 0	SC	68	>4 0	>4/2
2 0	SC	50		
1 0	SC	30		
DDS				
1 0	OS	92		
0 6	OS	69	0 25	
0 4	OS	41		
1 0	SC	87	0 25	1/2
0 5	SC	49		



in the bile indicated as high a concentration as 500 mg. per 100 cc. at 1 to 3 hours after the administration of the compound and 16 mg. per 100 cc. 24 hours later.

Thus it may be concluded that Promin is better absorbed than Sulphetrone; that both drugs are apparently metabolized to DDS when given orally; that the low blood levels following the oral administration of hydroxyethyl are not due to poor absorbability but rather to a preferential localization of the compound in certain tissues and organs of the body.

TABLE 9

*Activity in Guinea Pig Tuberculosis. 0.5 Mg. H37 Rv I.P. Treatment Day after Infection and Continued 80 Days*

DATE OF INOCULATION	NUMBER OF ANIMALS	THERAPY, MG/KG/DAY		MORTALITY PER CENT	AVERAGE WEIGHT GAIN	AVERAGE T.B. INDEX*	CHEMOTHERAPEUTIC EFFECTIVENESS†
		Sulfone orally	Streptomycin intramuscularly				
November, 1947	10	0	0	80	Gm 40	15.5	
	10	Hydroxyethyl-300	0	10	118	6.2	2.5
	10	0	20	10	276	1.5	10.3
	10	Hydroxyethyl-100	20	0	304	0.8	19.4
June, 1948	15	0	0	86	13	12.2	
	15	Sulphetrone-100	0	53	78	8.6	1.4
	15	Sulphetrone-500	0	66	10	9.9	1.2
	15	0	5	27	108	6.5	1.9
	15	0	25	7	204	2.0	6.1
	15	0	50	7	188	0.8	15.2
	15	Sulphetrone-100	5	0	175	3.6	3.4
	15	Sulphetrone-500	5	7	184	3.6	3.4
	15	Sulphetrone-100	25	0	240	1.3	9.4
	15	Sulphetrone-500	25	0	248	0.7	17.4

\* Average tuberculous involvement for the group, each animal being graded 0 to 20 according to the extent of lesions in (a) omentum and mesenteric glands (b) spleen (c) liver (d) peritoneum, kidneys and testes (e) lungs and mediastinal glands, each graded 0 to 4 on the basis of no visible lesions, slight, moderate, generalized, or extensive.

† Average TB index of controls/treated.

*Chemotherapeutic activity:* This was studied in experimental pneumococcus infection in mice and experimental tuberculosis in guinea pigs.

Brownlee and associates (4) state that Sulphetrone was inactive in experimental pneumococcus infection in mice. In our experience with monosubstituted derivatives of DDS, such compounds have usually shown considerable activity, frequently comparable with that of DDS, and because of their lower toxicity such compounds have often shown a more favorable chemotherapeutic index (9). In the case of the hydroxyethyl compound 50 per cent survival of

infected mice<sup>8</sup> was obtained with a total dose of 3.0 Gm per Kg orally and 2.0 Gm per Kg subcutaneously, suspended in olive oil, when given in 8 divided doses over a period of 4 days. In normal mice, a single dose of 8.0 Gm per Kg orally and 4.0 Gm per Kg subcutaneously failed to kill any animals. In the case of the parent substance DDS, approximately 0.5 Gm per Kg protected 50 per cent of infected mice when given in 8 divided doses over a period of 4 days, but the single dose of 0.25 Gm per Kg killed about 50 per cent of normal mice, whether given orally or subcutaneously. Thus the chemotherapeutic ratio of hydroxyethyl ( $LD_{50}/SD_{50}$ ) is more than 4 to 6 times greater than that of DDS. These data are shown in table 8.

The results obtained in experimental tuberculosis in guinea pigs are summarized in table 9. These data concern the activities of Sulphetrone and hydroxyethyl when used alone or in combination with streptomycin. The hydroxyethyl compound was used at the relatively low dose levels of 100 and 300 mg per Kg because of the limited supplies at the time this work was done. The Sulphetrone experiments were so planned as to give some information on the question as to which is the more critical, streptomycin or the supplementary sulfone, in combined therapy. The results indicate greater activity for hydroxyethyl than Sulphetrone when used alone, and potentiation of action in the case of the hydroxyethyl compound, comparable with that reported previously for Promin and other sulfones (3, 10). An additive effect in the instance of Sulphetrone was obtained when used with the small dose of 5 mg per Kg per day of streptomycin. When used with the larger dose of streptomycin, 25 mg per Kg per day, some potentiation of action was obtained. The chemotherapeutic effectiveness of 25 mg per Kg streptomycin plus 500 mg per Kg Sulphetrone was somewhat greater than that of double the dose of streptomycin when used alone.

#### SUMMARY AND CONCLUSIONS

A comparative study is presented of the pharmacologic and chemotherapeutic properties of (1) 4,4'-diaminodiphenylsulfone (DDS), (2) Promin, (3) Sulphetrone and (4) 4-amino-4'- $\beta$ -hydroxyethylaminodiphenylsulfone (hydroxyethyl).

The intravenous toxicity of Promin and Sulphetrone in rats is almost identical if computed on the basis of DDS equivalent.

The oral toxicity of Sulphetrone and hydroxyethyl is much less than that of Promin. The low toxicity of Sulphetrone appears to be due to poor absorbability.

The blood levels following oral administration of hydroxyethyl are relatively low. This is not due to poor absorbability but rather to a preferential localization of the compound in certain organs and tissues of the body, *e g*, liver, kidney, lungs, and spleen. About 50 per cent of the dose administered is excreted in the urine in 24 hours, and an undetermined but appreciable amount, possibly 25 per cent, is eliminated in the bile.

<sup>8</sup> Mice of 18 to 22 Gm were used and the infecting dose was 0.5 cc of  $10^{-6}$  dilution of a six hour broth culture of type I pneumococcus given intraperitoneally, which kills all controls within 24 hours (9).

There is evidence to indicate that Promin and Sulphetrone are metabolized in the body to the parent substance DDS, there is evidence that hydroxyethyl is not metabolized to DDS

Hydroxyethyl has a good chemotherapeutic activity in experimental pneumococcus infection in mice. Its activity in experimental tuberculosis in guinea pigs compares favorably with Promin. Like Promin it potentiates the action of streptomycin. Sulphetrone has a lower activity when used alone and, when used with 5 mg per Kg per day of streptomycin, the effect was additive. When used with the large dose of 25 mg per Kg per day of streptomycin, some potentiation of action was obtained.

#### SUMARIO Y CONCLUSIONES

##### *La Accion Farmacológica y Quimioterapéutica de Algunas Nuevas Sulfonas y de la Estreptomicina en la Tuberculosis Experimental*

Este estudio comparativo versa sobre las propiedades farmacológicas y quimioterapéuticas de (1) la 4,4'-diaminodifenilsulfona (DDS), (2) la promina, (3) la sulfetrone, y (4) la 4-amino-4'- $\beta$ -hidroxietilaminodifenilsulfona (hidroxietilo).

La toxicidad endovenosa de la promina y la sulfetrone en las ratas es casi idéntica si se computa a base de equivalencia en DDS.

La toxicidad por vía oral de la sulfetrone y el hidroxietilo es mucho menor que la de la promina. La poca toxicidad de la sulfetrone parece deberse a mala absorbibilidad.

Los tenores sanguíneos consecutivos a la administración oral del hidroxietilo son relativamente bajos, lo cual no se debe a mala absorbibilidad sino más bien a localización preferente del compuesto en ciertos órganos y tejidos, por ej., hígado, riñones, pulmones y bazo. Aproximadamente 50 por ciento de la dosis administrada se excreta en la orina en veinticuatro horas y una cantidad indeterminada, pero apreciable, posiblemente 25 por ciento, es eliminada en la bilis.

Hay datos indicativos de que, en el cuerpo, la promina y la sulfetrone se metabolizan en la sustancia matriz, DDS, habiendo también datos de que no sucede otro tanto con el hidroxietilo.

El hidroxietilo muestra buena actividad quimioterapéutica en la infección neumocócica experimental en los ratones. Su actividad en la tuberculosis experimental del cobayo compárase favorablemente con la de la promina, y lo mismo que ésta, realza la acción de la estreptomicina. La sulfetrone muestra menos actividad cuando se usa por sí sola, y usada con 5 mg diarios de estreptomicina por kg, mostró efecto aditivo. Usada con una dosis masiva de 25 mg diarios de estreptomicina por kg, obtuvo alguna potenciación del efecto.

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# NEOMYCIN ACTIVITY UPON MYCOBACTERIUM TUBERCULOSIS AND OTHER MYCOBACTERIA<sup>1 2, 3</sup>

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## INTRODUCTION

Before a new antimicrobial agent can be considered at the present time as having chemotherapeutic potentialities, it must possess the following properties

1 It must be active, not only *in vitro* but also *in vivo*, against certain specific organisms, it is desirable that such activity be greater than that of other agents now recognized as useful or as promising

2 It must be active against those strains of important disease-producing organisms which are not sensitive or which have become resistant to presently accepted chemotherapeutic agents

3 It should not favor the development of resistance among sensitive bacteria, or should at least permit lesser development of such resistance than existing agents, or it should act synergistically with those agents

4 It should not be toxic to animals, or at least it should be no more toxic than agents now used for chemotherapeutic purposes

These four postulates can be enlarged and others added, as regards both the substances that possess antimicrobial properties, whether antibiotics or synthetic compounds, and the organisms which are thus affected, whether bacteria, fungi, protozoa, or viruses

During the last five years, or since the isolation of streptomycin in this laboratory, several new agents were obtained that at first appeared promising but which were later discarded because they did not meet the above requirements. This is true, for example, of grisein (1) and streptothricin VI (2). The same is true of other agents isolated in different laboratories.

Because of its marked antimycobacterial properties, streptomycin has so far proved to be the most promising antibiotic in the treatment of infections caused by *Mycobacterium tuberculosis*. It possesses certain serious limitations, however, notably, first, the ease with which sensitive bacteria develop resistance to it and, second, certain toxic manifestations. It becomes, therefore, essential to find new agents which would be less favorable to the development of resistance among bacteria, less toxic, and possibly more potent than streptomycin.

The isolation of such an agent, designated as *neomycin*, recently was announced (3, 4).

On the basis of extensive laboratory studies against various bacteria, including

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<sup>3</sup> Some of the data reported in this paper were presented before the seventh Streptomycin Conference, Veterans Administration, held in Denver, Colorado, on April 23, 1949

both saprophytic and pathogenic mycobacteria, as well as of experimental studies in animals against various gram-positive and gram-negative bacteria (exclusive of *M. tuberculosis*), neomycin appears to meet the above requirements (1) It is more active than streptomycin against both the saprophytic *Mycobacterium* 607 and pathogenic strains of *M. tuberculosis* (2) It is as active against the streptomycin-resistant strains of these organisms as against the sensitive ones (3) It favors to a far lesser degree than does streptomycin the development of resistant strains of mycobacteria although, on prolonged serial transfer of large numbers of cells, a considerable increase in resistance may be obtained (4) It is characterized by a relatively low toxicity to animals

The degree of toxicity of neomycin, in comparison with that of streptomycin, has not yet been fully established, nor has its *in vivo* activity against the tuberculosis organism

TABLE 1

*Comparative Effects of Neomycin and Streptomycin upon the Growth of Different Mycobacteria*

Growth inhibition in units per ml after 14 days' incubation

TEST ORGANISM	NEOMYCIN	STREPTOMYCIN
<i>M. avium</i>	0 1-0 3	10 0
<i>M. tuberculosis</i> H37 Rv	0 2-1 0	1 0-5 0
<i>M. tuberculosis</i> H37 RvR*	0 2-1 0	>5,000
<i>Mycobacterium</i> 607	0 1	0 2-0 4
<i>Mycobacterium</i> 607R*	0 25	>300

\* R = streptomycin-resistant strain

The results of the following experiments tend to substantiate the foregoing conclusions

#### EXPERIMENTAL

*Antimycobacterial properties of neomycin* The relatively high potency of neomycin against mycobacteria may be seen in table 1. Different organisms belonging to this group vary greatly, however, in their sensitivity to this antibiotic, the saprophytic *Mycobacterium* 607 being the most sensitive. When pathogenic strains of *M. tuberculosis* were tested in several laboratories, somewhat different results were obtained. This is quite natural, since one must allow not only for the origin of the culture, its past history and method of testing, but also the individual idiosyncrasy of the observer. In general, the various cultures were more sensitive to neomycin than to streptomycin. Only seldom was a streptomycin-resistant culture of *M. tuberculosis* found to be somewhat more resistant to neomycin than the corresponding streptomycin-sensitive culture. Such differences were only minor in nature, however, and may have resulted from variations in procedure. Freshly isolated cultures of *M. tuberculosis* were also found to be more sensitive to neomycin than to streptomycin (table 2). This was true especially of the streptomycin-resistant strains which

showed in this case no difference in sensitivity to neomycin as compared to the streptomycin-sensitive cultures

When the antimycobacterial properties of neomycin were compared further with those of streptomycin and of streptothricin against both saprophytic and pathogenic strains, certain very striking differences were obtained (table 3)

TABLE 2

*Comparative Effects of Neomycin and Streptomycin upon Freshly Isolated Strains of M. tuberculosis*

(F. Heilman and G. M. Needham)

STRAIN NUMBER	SOURCE OF CULTURE	AMOUNT INHIBITING GROWTH*	
		Streptomycin	Neomycin
		$\gamma$ per ml	units per ml
100	Sinus left hip	1 to 5†	<0.5
500	Sinus left flank	1 to 5	<0.5
575	Bladder	>100	<0.5
910	Gastric	1 to 5	<0.5
209	Sputum	1 to 5	<0.5
684	Urine	>100	<0.5

\* Tests made in liquid Proskauer and Beck's medium fortified with 0.25 per cent bovine albumin (fraction V)

† 1 to 5 = more than 1 and less than 5  $\gamma$  required to inhibit growth, >100 = growth not inhibited by 100  $\gamma$

TABLE 3

*Influence of Continuous Incubation upon the Antimycobacterial Properties of Different Antibiotics*

ORGANISMS	UNITS OF ANTIBIOTIC REQUIRED TO INHIBIT GROWTH PER MILLILITER OF CULTURE IN DUBOS TWEEY MEDIUM*					
	Neomycin		Streptomycin		Streptothricin	
	Days of incubation					
	7	14	7	14	7	14
<i>Mycobacterium</i> 607	0 1	0 1	0 3	0 3-0 6	0 75	2
<i>Mycobacterium</i> 607R	0 1-0 25	0 25	200	300	1 0	2
	14	28	14	28	14	28
<i>M tuberculosis</i> H37 Rv	0 5-1 0	1 5-2 0	2	4	10	20
<i>M tuberculosis</i> H37 RvR	1 0	1 0	>5,000	>5,000	10	20

\* Dilution of inoculum = 1:1,000

Neomycin was found to possess far superior properties as an antituberculous agent than the other two antibiotics. This expressed itself in at least three distinct ways: (a) neomycin was the most active of the three antibiotics when tested against both saprophytic and pathogenic mycobacteria, (b) neomycin was as active upon the streptomycin-resistant as upon the streptomycin-sensitive

mycobacteria, (c) upon continued incubation of the cultures in the presence of the three antibiotics, the tendency toward the development of resistance to neomycin was less than to the other two antibiotics

A more detailed study has now been made of the course of growth of both streptomycin-sensitive and streptomycin-resistant strains of *M. tuberculosis* H37 Rv in the presence of three different antibiotics, in order to establish the course

TABLE 4

*Comparative Tuberculostatic Effects of Neomycin, Streptomycin and Aureomycin upon the Growth of M. tuberculosis H37 Rv*

Turbidimetric readings in Dubos-Tween medium

UNITS PER ML.	NEOMYCIN, INCUBATION IN DAYS				γ PER ML	STREPTOMYCIN, INCUBATION IN DAYS				γ PER ML	AUREOMYCIN, INCU- RATION IN DAYS		
	4	9	16	25		4	7	14	25		4	7	14
0	15	23	78	225	0	10	21	96	268	0	9	17	40
0.1	0	15	79	244	0.1	5	25	101	256	0.5	7	17	96
0.5	0	0	38	155									
1.0	0	0	11	120	1.0	0	0	11	101	5.0	6	9	64
2.0	0	0	0	0	2.0	0	0	0	37	10.0	0	6	22
					4.0	0	0	0	0	50.0	0	0	0

TABLE 5

*Comparative Tuberculostatic Effect of Different Antibiotics upon the Growth of Mycobacterium 607*

Turbidimetric readings in Dubos-Tween medium

UNITS PER ML	NEOMYCIN, INCUBATION IN DAYS			γ PER ML	STREPTOMYCIN, INCUBATION IN DAYS		
	2	4	16		2	4	14
0	35	80	288	0	24	65	282
0.1	0	0	0	0.1	20	47	185
0.25	0	0	0	0.3	0	0	180
0.5	0	0	0	0.5	0	0	0
UNITS PER ML	STREPTOTHRICIN, INCUBATION IN DAYS			γ PER ML	AUREOMYCIN, INCUBATION IN DAYS		
	2	4	14		2	4	14
0	28	98	270	0	48	82	245
0.1	15	65	260	0.5	33	75	248
0.5	0	5	180	5.0	0	12	216
1.0	0	0	55	10.0	0	0	160

of development of resistance. Only the growth of the sensitive strains is reported in table 4. The amount of neomycin required to inhibit completely the growth of both strains of this organism was 1.0 to 2.0 units per ml, after a prolonged incubation period. Although even smaller concentrations of the antibiotic were found to cause partial inhibition of growth, this effect was later overcome, either because of the gradual adaptation of the culture or because of



development of the more resistant cells. Beyond the concentration of 2 units per ml, however, no growth appeared even after four weeks' incubation of cultures. Streptomycin allowed the more rapid adaption of the organism to the antibiotic, and the final inhibiting concentration was about twice as high as for neomycin. The third antibiotic used in this experiment, aureomycin, showed up rather poorly in comparison with the other two.

Similar results were obtained when the action of several antibiotics against the saprophytic culture *Mycobacterium* 607 was measured (table 5). The growth of this organism was completely inhibited by 0.1 unit per ml of neomycin, no resistance developed even after prolonged incubation. There was comparatively little difference in the effect of neomycin upon the streptomycin-sensitive and streptomycin-resistant strains, the latter showing some growth at 0.1 unit per ml after prolonged incubation of the culture, but not above that concentration. Streptomycin was only about one-third as active upon the saprophytic mycobacterium as neomycin, the activity of streptomycin being less than one-tenth, and of aureomycin less than one-hundredth.

In further studies of the effect of neomycin upon the growth of mycobacteria, it was found that the size of inoculum was of considerable importance within certain limits. When an inoculum of  $1 \times 10^8$  was used, 0.2 unit per ml of neomycin was required to inhibit the growth of *Mycobacterium* 607, when the inoculum was  $1 \times 10^{10}$ , growth was completely inhibited by 0.1 unit per ml. When repeated transfers, using approximately 122,000 cells, to fresh medium were made from those cultures in which growth occurred in presence of neomycin, only a very limited increase in resistance took place. These results emphasize further the fact that neomycin favors much less the development of resistance among mycobacteria than any of the other antibiotics tested.

A series of plates containing varying concentrations of neomycin were inoculated with large numbers of viable cells of *Mycobacterium* 607 (2 million cells per plate). Only 0.1 unit per ml permitted growth. When pieces of agar were removed after seven days' incubation and placed in fresh liquid medium, growth occurred from the plates containing 0.1 unit per ml after two days, 0.5 unit per ml to 1.0 unit per ml after six days. When such pieces of agar were removed after fourteen days' incubation and placed in fresh liquid medium, growth occurred only from the 0.1 unit per ml plates, but not from those containing the higher concentrations of the antibiotic. This points to the marked bactericidal effects of neomycin. These observations were confirmed in various subsequent quantitative studies. In a more detailed study, the mycobactericidal properties of neomycin, streptomycin, and streptomycin were compared. Washed suspensions of mycobacteria were used and the number of cells was measured by the plate method. It was found that neomycin was the most bactericidal of the three antibiotics and streptomycin the least.

*Comparative effects of streptomycin and neomycin upon Mycobacterium 607*  
Although the saprophytic *Mycobacterium* 607 behaves in its physiology, rate of growth, and other properties in a distinctly different manner from the pathogenic mycobacteria, it lends itself readily to detailed studies of the type planned here.

Whenever possible, such experiments were finally checked by the use of pathogenic forms

It has been shown that *Mycobacterium* 607 is sensitive to 0.1 unit of neomycin. This varies somewhat depending on the medium and the length of incubation period. In conformity with the above results, it was found that this organism is not only more sensitive to neomycin than to streptomycin, but that it also allows less development of resistant strains, as may be seen in figure 1. The ratio of sensitivity of *Mycobacterium* 607 to streptomycin, as compared to neomycin, is 0.4:0.1, the latter antibiotic being thus four times as effective as streptomycin against this organism.

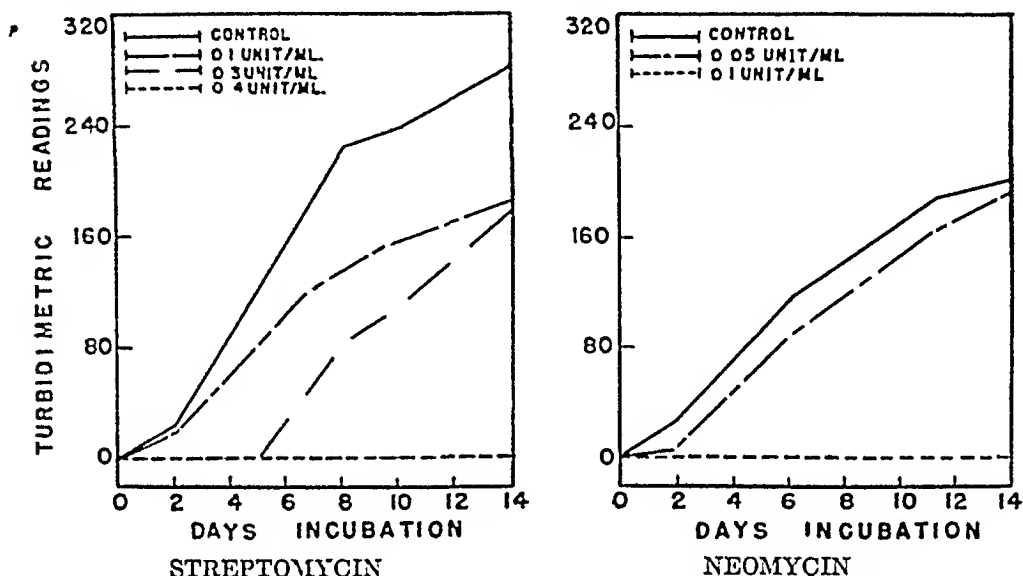


FIG 1 Inhibition of growth of *Mycobacterium* 607 by different concentrations of streptomycin and neomycin

That neomycin is as effective upon the streptomycin-resistant strain of *Mycobacterium* 607, namely 607R, as upon the sensitive one is illustrated in figure 2. The culture used in this experiment was not made absolutely resistant to streptomycin, since it was usually inhibited by 400  $\gamma$  per ml of this antibiotic, as compared to the sensitivity of the normal strain (0.4  $\gamma$  per ml), it may be considered relatively resistant. The resistance of this strain to neomycin is only slightly greater, namely 0.2 unit per ml as compared to 0.1 unit per ml in the case of the streptomycin-sensitive strain.

*Effect of inoculum upon the sensitivity of Mycobacterium 607 to neomycin*  
It was pointed out above that neomycin does not favor the rapid development of resistant strains. In these studies, a 7 day old culture of the organism was diluted one thousand fold with Dubos-Tween medium, and turbidimetric readings were made daily with a Klett-Summerson photometer. To test the effect of inoculum upon the activity of neomycin, a 5 day old culture of *Mycobacterium*

607 was diluted with the Dubos-Tween medium to 1 10, 1 100, 1 1,000. Duplicate tubes were incubated and readings made daily. The results (figure 3)

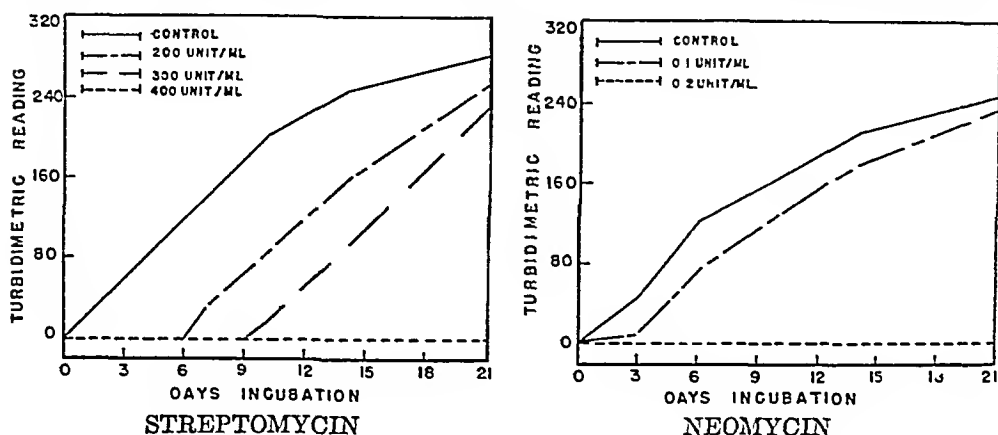


FIG 2 Inhibition of growth of streptomycin-resistant strain of *Mycobacterium* 607 (607R) by different concentrations of streptomycin and neomycin

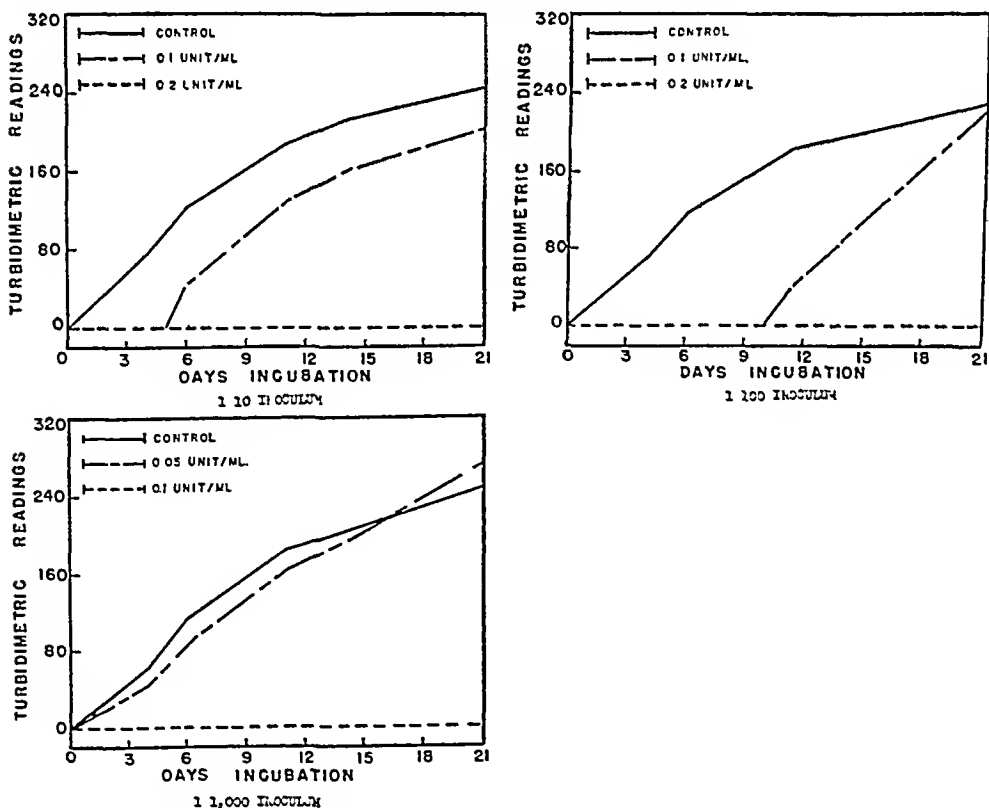


FIG 3 Effect of inoculum upon growth inhibition of *Mycobacterium* 607 by neomycin

show that in the 1 1,000 inoculum the limiting effective concentration of neomycin is 0.1 unit per ml, whereas the 1 10 inoculum requires 0.2 unit per ml for growth inhibition. The 1 100 inoculum fell between

When repeated transfers were made from the tubes giving growth of the organism in the presence of 0.05 unit per ml and 0.1 unit per ml of neomycin into fresh tubes containing varying concentrations of the antibiotic, no marked

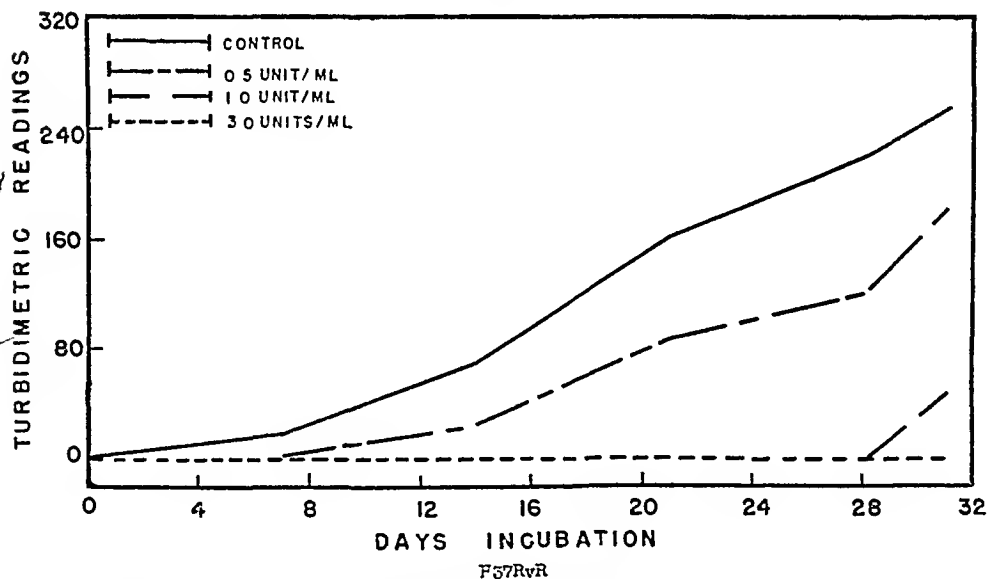
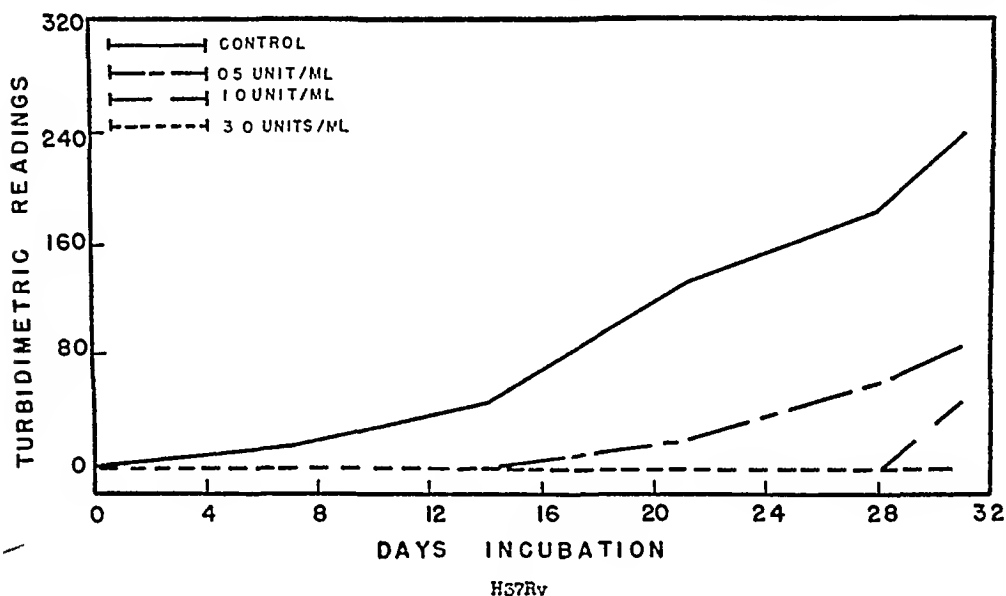


FIG 4 Effect of neomycin upon the growth of streptomycin-sensitive strains and streptomycin-resistant strains of *Mycobacterium tuberculosis*

increase in resistance was obtained. The slight increase frequently observed usually expressed itself in an earlier initiation of growth at a given limiting zone of inhibition, i.e., growth in presence of 0.1 unit per ml was now observed first after one to three days' incubation as compared to the previous six to eleven days. The 1:1,000 dilution of the culture which was grown in the presence of neomycin

required 0.2 unit per ml for inhibition of growth in place of the original 0.1 unit per ml. In general, when large numbers of *Mycobacterium* 607 were placed in contact with neomycin and with streptomycin in glycerol-nutrient agar media, neomycin proved to be much more bacteriostatic than streptomycin. In one experiment 0.5 unit per ml of neomycin completely inhibited the growth of

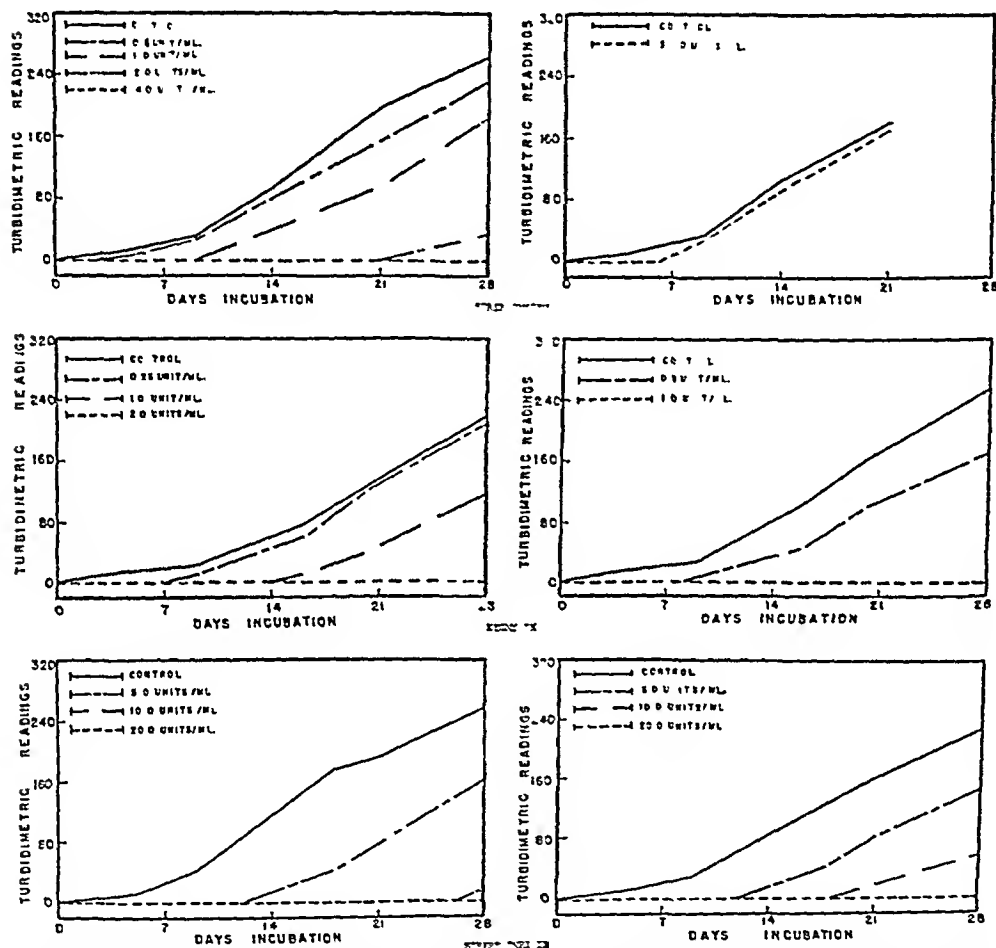


FIG. 5. Inhibition of growth of streptomycin-sensitive (left) and streptomycin-resistant (right) strains of *M. tuberculosis* H37 Rv by 3 basic antibiotics: upper—streptomycin, middle—neomycin, lower—streptomycin.

36,300,000 cells, whereas 1.0  $\gamma$  per ml of streptomycin did not inhibit one-hundredth that number of cells.

*Effect of neomycin and other antibiotics upon the growth of M. tuberculosis H37 Rv.* The amount of neomycin required to inhibit growth of the pathogenic *M. tuberculosis* H37 Rv and of the streptomycin-resistant H37 RvR is somewhat greater than that necessary to inhibit growth of the saprophytes. This amount was reported from different laboratories to vary from 0.2 unit per ml to 2.0 units per ml. Here again, the incubation period was found to be very important, as

may be seen in figure 4. After fourteen days' incubation, 0.5 unit per ml was found to suffice for inhibition of growth, after twenty-eight days, however, one unit was required, with longer periods of incubation, even higher concentrations may become necessary. This is true of both the streptomycin-sensitive and streptomycin-resistant strains.

Comparison of the effect of neomycin upon *M. tuberculosis* H37 Rv with that of streptomycin and streptothricin (figure 5) brings out several important points which can be summarized as follows: (a) neomycin is at least equally effective upon the streptomycin-resistant as upon the streptomycin-sensitive strain, (b) neomycin is about twice as active upon *M. tuberculosis* as is streptomycin, (c) streptothricin is the least effective of the three antibiotics. Although streptothricin is also effective upon the streptomycin-resistant strains, nearly ten times as many units or more are required, as compared to neomycin, to bring about the same degree of inhibition. These results can lead to only one conclusion, namely, that of the three basic antibiotics active upon *M. tuberculosis*, neomycin is the most potent and streptothricin the least.

For the sake of completeness, it may be of interest to record here certain pertinent data on the effects upon mycobacteria of another antibiotic produced by a member of the genus *Streptomyces*, namely aureomycin, as shown in some of the tables reported previously. Whereas streptomycin inhibited the growth of *Mycobacterium* 607 for four days when the concentration was 0.2  $\gamma$  per ml and for fourteen days when 0.4  $\gamma$  per ml, it took 5  $\gamma$  per ml or 25 times as much aureomycin to produce the same inhibition in two days, and 50  $\gamma$  per ml or 125 times as much to inhibit the growth of the organism for fourteen days. Aureomycin was found to be effective alike against the streptomycin-resistant and the streptomycin-sensitive strains of *Mycobacterium* 607.

The growth of *M. tuberculosis* H37 Rv was inhibited by 1  $\gamma$  per ml of streptomycin during seven days, 2  $\gamma$  per ml were required for growth inhibition in twenty-one days, and 4  $\gamma$  per ml for complete inhibition during twenty-eight days of incubation. In the case of aureomycin, however, 10  $\gamma$  per ml were required to inhibit growth of the organism in four days and 50  $\gamma$  per ml for growth inhibition in seven days, or 10 to 50 times the amount of streptomycin. Because of these limited effects *in vitro*, aureomycin does not appear to be an antituberculous agent of promise.

*Toxicity and in vivo activity of neomycin.* Treatment of experimental tuberculosis requires larger amounts and more repeated administration than treatment of ordinary infections caused by gram-negative and gram-positive bacteria. In the case of the latter organisms, including such forms as *Staphylococcus aureus*, *Salmonella schottmüller*, and *Salmonella pullorum*, it was found that a single dose of 100 units by subcutaneous administration in mice or upon the allantoic membrane in chick embryos was sufficient to bring about protection. Frequently, a much smaller dose was effective. The preparations used for this purpose showed a toxic level of 2,000 to 5,000 units per 18 to 20 Gm mouse, or a ratio of 20 to 50 between toxicity and therapeutic activity.

In an effort to produce larger amounts of neomycin, especially in changing the

composition of the medium to obtain higher potency material, certain toxic preparations were encountered. This complicated somewhat the effort made to obtain immediate information concerning its *in vivo* antituberculous activity. Before the product is standardized, before the toxic contaminations have been eliminated, before suitable dosages have been worked out, it is difficult to say how this new antibiotic will fit into the therapy of tuberculosis.

#### SUMMARY

The results of a comparative study of the antimycobacterial properties of a new antibiotic, neomycin, and certain other antibiotics, including streptomycin, are presented. These results permit the following conclusions:

1 Neomycin is more active than other antibiotics against both pathogenic and saprophytic mycobacteria.

2 Neomycin is just as active against the streptomycin-sensitive as against the streptomycin-resistant mycobacteria.

3 Neomycin does not allow a rapid development of resistance among the mycobacteria as does streptomycin. Repeated transfers of the organism to media containing neomycin brought about only a slight increase in resistance.

4 The amount of neomycin required to inhibit the growth of mycobacteria depends upon nature of organism, size of inoculum, and length of incubation period. The saprophytic *Mycobacterium* 607 is inhibited by about 0.1 unit per ml and the pathogenic *M. tuberculosis* by 0.2 to 1.0 unit per ml.

5 Results of the *in vivo* studies against tuberculosis in experimental animals are still insufficient to justify broad conclusions. Neomycin is highly effective against the ordinary pathogenic gram-negative and gram-positive bacteria, the activity dose being one-twentieth to one-fiftieth that of the toxic dose. This is true for both streptomycin-sensitive and streptomycin-resistant organisms. The evidence further suggests that neomycin is also more active against those bacteria than is streptomycin.

#### SUMARIO

##### *Acción de la Neomicina sobre el Mycobacterium tuberculosis y Otras Micobacterias*

Los resultados expuestos derivan de un estudio comparativo de las propiedades antimicobacterianas de un nuevo antibiótico, la neomicina, y de ciertos otros antibióticos, incluso la estreptomina, cabiendo sacar las siguientes conclusiones:

1 La neomicina es más activa que otros antibióticos contra las micobacterias, tanto patógenas cuanto saprofitas.

2 La neomicina es igualmente activa contra las micobacterias tanto estreptomina-sensibles cuanto resistentes.

3 La neomicina no permite, como la estreptomina, rápida formación de resistencia en las micobacterias. Los pases repetidos de los microbios a medios que contenían neomicina solo consiguieron leve aumento de la resistencia.

4 La cantidad de neomicina necesaria para inhibir el desarrollo de las mico-

bacterias depende de la naturaleza del microbio, la cantidad de inóculo y la duración del período de incubación. El saprofita *Mycobacterium* 607 is inhibido aproximadamente por 0.1 unidad por ml y el patógeno *M. tuberculosis* por 0.2 a 1.0 unidad por ml.

5. Los resultados de los estudios *in vivo* contra la tuberculosis en los animales de experimentación son todavía insuficientes para sacar amplias conclusiones. La neomicina es altamente eficaz contra las ordinarias bacterias patógenas gram-negativas y positivas, siendo la dosis activa de una vigésima a una centésima de la tóxica, lo cual reza tanto con los microbios estreptomycin-sensibles como con los resistentes. Los datos disponibles indican además que la neomicina, por vía oral, es también más activa que la estreptomycin contra dichas bacterias.

#### Acknowledgment

The authors wish to express their sincere appreciation to Dr. F. Heilman of the Mayo Clinic for permission to use the data incorporated in table 2.

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# THE USE OF THE MOUSE IN A STANDARDIZED TEST FOR ANTITUBERCULOUS ACTIVITY OF COMPOUNDS OF NATURAL OR SYNTHETIC ORIGIN<sup>1</sup>

## I Choice and Standardization of Culture

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### INTRODUCTION

As dramatic successes have followed one another in the discovery of substances curative in most acute and some chronic bacterial infections, attention has been focused on those infections where such success has not been so complete. One such infection is tuberculosis. Although the discovery of streptomycin (1) has provided a drug of the greatest importance, most investigators and clinicians feel that it, or it alone, is not the final word in the therapy of this infection.

In the investigation of large series of substances for action *in vivo* against the tubercle bacillus, the use of a satisfactory experimental animal is of prime importance. In the past the animal of choice has been the guinea pig, although the rabbit and the mouse have also been used. Some investigators, indeed, believe that the results of such *in vivo* tests are only valid for man if carried out in the highly susceptible guinea pig. The present writers have been led to abandon this latter animal in favor of the mouse for the following reasons. Work with mice in tuberculosis and other infections has shown the importance of the use of homozygous animals when few animals can be tested and when, for this and other reasons, uniformity of response is desirable. No ready source of homozygous guinea pigs is available while, on the other hand, many homozygous strains of mice are readily available. Since many of the drugs to be tested are in short supply, it is of the utmost importance to use a small animal, and in the fewest numbers which will give reproducible results. As will appear in the third paper of this series (2), using homozygous mice in groups of 10 per dose level, chronic toxicity tests and tests of therapeutic effectiveness, as well as *in vitro* tests, can be carried out with 20 grams or less of material. Furthermore, the use of the mouse entails a far lower immediate and continuing expense than does the use of a larger animal, since the initial cost is lower and mice can subsequently be housed and fed at appreciably lower cost than can guinea pigs. Finally, there is no evidence that the results of chemotherapy in tuberculosis of the guinea pig are a more certain guide to the usefulness of a given compound in man than are the results obtained in mice. Indeed the reverse appears actually to be the case.

A consideration of these facts has led us to an investigation of the use of the

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mouse for *in vivo* tests for chemotherapy of tuberculosis. The standardization and use of such a test will form the material for the subsequent series of reports.

#### LITERATURE

Although the first observation on the use of the mouse in experimental tuberculosis was made in 1884 by Koch (3), this animal has been, until recently, very little used. Since Raleigh and Youmans (4) have published a comprehensive review of the literature, mention will be made here only of such work as deals specifically with the relative virulence of *M. tuberculosis* var. *hominis*, var. *bovis*, and *Mycobacterium avium*.

Among the first to investigate the relative virulence for mice of the different types of *M. tuberculosis* was Römer (5) in 1903, who compared the virulence of 4 human and 5 bovine strains. Since only one of the human strains approached the bovine in virulence, he concluded that bovine strains were more virulent. Infection was more readily produced by intraperitoneal than by subcutaneous injection.

In the studies of the Royal Commission on Tuberculosis (6), although extensive experiments with many species of animals were carried out, very little work was done with the mouse. The two routes of injection used in the mouse experiments were the subcutaneous and intraperitoneal. In the few mice used, the dosage varied so greatly that no conclusion could be reached as to the relative virulence of human, bovine, and avian strains of *M. tuberculosis* for this animal.

Trommsdorff (7) in 1909 tested several bovine and human strains of *M. tuberculosis* by intravenous injection into mice and found the bovine strains more virulent. Peters (8) in 1912 injected mice intravenously with 1 mg. doses of 2 human and 2 bovine strains. Only 3 to 4 mice were used for each strain. Mice injected with the bovine strains died between 4 and 7 weeks while mice injected with the human strains showed relatively slight lesions in the organs when killed 8 to 9 weeks after injection. On the basis of these meager data, he concluded that the mouse could be used to differentiate human and bovine strains. Binder (9) injected 1 mg. doses of one human and one bovine strain intravenously into white mice. Six mice injected with the bovine strain died between the twenty-seventh and fifty-seventh days, while 7 mice injected with the human strain showed only a few discrete lesions when killed between the one hundred thirtieth and one hundred eighty-eighth days. The results of Trommsdorff, Peters and Binder, although obtained with small numbers of mice, are in agreement. On the other hand, Lange (10) in 1922, using 4 human and 3 bovine strains, injected mice intravenously with doses of 1.0, 0.1, 0.01, and 0.001 mg. and concluded that the virulence of the two types was the same. In this work also, the number of mice used was small, only 2 to 6 mice for each dose of culture.

Browning and Gulbransen (11) in 1926 tested the virulence for mice of 7 human and 6 bovine strains. Three mice only were used for each culture. The dose in all cases was 0.75 mg. injected intraperitoneally. In general, mice infected with the human strains lived longer than those infected with the bovine strains. Also, several human strains failed to produce infection whereas no failure occurred with the bovine strains.

Gunn, Nungester, and Hougen (12) in 1934, using recently isolated human, bovine, and avian strains, found mice equally susceptible to the human and bovine but resistant to avian strains. One mg. doses of human and bovine strains injected intraperitoneally gave average survival times respectively of 46 and 45 days. The average survival time following intravenous injection of smaller doses was much shorter. Avian bacilli never caused a fatal infection even when a large dose (1 mg.) was injected intravenously, but characteristic lesions were produced in the liver and spleen while the lungs were usually free of gross lesions.

Schwabacher and Wilson (13) in 1937 tested the virulence for mice of 2 human, 2 bovine and 4 avian strains. A dose of 200 million bacilli injected intravenously into 8 to 21 mice was used. The human and bovine strains were found to be equally virulent, all infected mice died, and the mean time of death was 25.5 and 32.3 days for the human strains and 22.5 and 30.9 for the bovine strains. The avian strains were less virulent and have produced

tion in virulence, approximately one-half the mice survived and the mean times of death for the 4 strains were 39.6, 57.5, 108.5, and 138.3 days

Stamatín and Stamatín (14) in 1939 carried out an extensive study of the virulence for white mice of recently isolated strains. Ten human strains and 9 variants, 10 bovine strains and 2 variants, and 4 avian strains were used. The cultures were injected intravenously in doses of 1.0, 0.1, 0.01, and 0.001 mg. Results with the human and bovine strains were similar with the larger doses but with the smallest dose (0.001 mg) the length of life was shorter and the lesions more severe in mice injected with the bovine strains. Avian strains were much less virulent than human or bovine strains.

Pagel (15) in 1940 observed that human and bovine strains when injected intracutaneously into mice induced more pronounced lesions than avian strains. Long and Vogt (16) in 1941 found no difference in the response of white mice to intraperitoneal injection of 1.0 mg doses of a human and a bovine (Ravenel) strain.

It is somewhat difficult to draw definite conclusions from the data presented by these investigators since no standard procedures were used. While there is disagreement in regard to the relative virulence for mice of human and bovine strains, it is clear that both possess far greater virulence than the avian type. There are undoubtedly strain differences within types but it appears that bovine strains may be universally more virulent than human strains.

In the present series of papers, investigation leading to the establishment of a standardized test in mice for antituberculous activity is outlined. In evolving such a test the first consideration was choice of a satisfactory strain of *M. tuberculosis*. Such a strain must possess sufficiently high and constant virulence to give reproducible results. The choice of culture, dosage, and methods of maintenance are presented in the first paper of this series.

#### MATERIALS AND METHODS

**Cultures** Two strains of *M. tuberculosis* var. *hominis*, H37 Rv and R, and two strains of var. *bovis*, Ravenel and D4, were used in the present study. The H37 Rv strain was obtained from Mr. William Steenken, Jr., Trudeau, New York, and the R strain from Dr. Arnold Rich, the Johns Hopkins Hospital, Baltimore, Maryland. The Ravenel strain was obtained from Dr. Max Lurie, Henry Phipps Institute, Philadelphia, Pennsylvania, and the D4 strain from Dr. Harold J. White, American Cyanamid Co., Stamford, Connecticut, who had obtained it from Dr. Maurice L. Cohn, National Jewish Hospital, Denver, Colorado.

**Medium** Stock cultures were kept stored at 3°C on the Jensen and Holmes modification of Loewenstein's medium (17). Because of the difficulty experienced in obtaining a sterile medium, even with inspissation repeated on three successive days a preliminary sterilization of the potato flour was introduced. When this was done, one inspissation only was sufficient to give a sterile medium. The formula is given below.

#### *Loewenstein Medium*

##### (a) Mineral salt solution

Anhydrous potassium sulphate	1.2 Gm
Anhydrous magnesium sulphate	0.12 Gm
Magnesium citrate	0.3 Gm
Asparagine	1.8 Gm
Glycerine	6 ml
Distilled water to make	300 ml

Dissolve and sterilize at 100°C for two hours.

(b) Sterilize 15 Gm potato flour in a 2 liter Erlenmeyer flask in hot air oven at 130°C for two hours. When cool, add mineral salt solution and place in boiling water bath. Agitate constantly until a soft paste is produced (20 to 25 minutes). Place in 56°C water bath for one hour.

(c) Wash 10 to 12 fresh eggs and place in 70 per cent alcohol for ten to fifteen minutes. Mix eggs in sterile Waring blender for one half minute and add to mineral salt starch solution.

(d) Add 10 ml of a 2 per cent Malachite green solution which has been incubated at 37°C overnight. Mix thoroughly and filter through sterile gauze. Tube and place in 3-milliliter aliquots at 20°C. Reduce temperature up slowly to 75°C (this should take about one hour). Hold at 75°C for forty five minutes. No subsequent sterilization is necessary.

Cultures to be used for mouse injection were grown, after the manner of Dubos (18), in a liquid medium containing Tween 80 and serum albumin. As a basic medium, Kirchner's (19) synthetic medium to which was added 0.05 per cent Tween 80 to induce diffuse growth and 0.1 per cent human serum albumin, was used. A 25 per cent solution of human serum albumin in distilled water, sterilized by filtration, was added to the previously autoclaved Kirchner Tween 80 medium in an amount sufficient to make a final concentration of 0.1 per cent serum albumin. The formula for the Kirchner medium is as follows:

#### *Kirchner Synthetic Medium*

NaHPO <sub>4</sub>	3.0 Gm
KH <sub>2</sub> PO <sub>4</sub>	4.0 Gm
MgSO <sub>4</sub>	0.6 Gm
Sodium citrate	2.5 Gm
Asparagine	5.0 Gm
Iron ammonium citrate	0.05 Gm
Glycerine	20 ml
Distilled water	1,000 ml

*Maintenance of cultures.* The cultures to be used for mouse injection were grown in 50 ml Erlenmeyer flasks containing 20 ml of Kirchner Tween 80 serum albumin medium. An inoculum of 2 ml of a culture grown in the same manner was used. Cultures were incubated for five days at 37°C.

*Mice.* CF-1 albino mice weighing 16 to 20 Gm were used in all experiments. The injections were made by the intravenous route. Cultures were diluted so that the required dose was contained in a volume of 0.5 ml since it was believed that this volume ensured a more constant dose than could be achieved by the use of smaller volumes such as 0.1 or 0.2 ml. Throughout this paper the dosage will be given in terms of undiluted culture, that is, if the dose used is 0.5 ml of a 1:10 dilution it will be given as 0.05 ml of undiluted culture. The mice were observed daily and group weights were taken at intervals of three to four days. Autopsies were performed on all mice to exclude the possibility of death from causes other than tuberculosis.

In the experiments which follow, the 50, or calculated 50 per cent survival time, was used in all virulence studies. The 50 per cent survival times were calculated from time mortality curves according to the method described in the second paper of this series (20).

## RESULTS

### *Choice of Medium*

*Experiments in vitro.* The announcement by Dubos (18) and Dubos and Davis (21) of a medium in which tubercle bacilli grew rapidly and diffusely, and yet retained their acid-fast characteristics and virulence, offered the means of simplifying both the cultivation of tubercle bacilli and the standardization of suspensions to be used in experimental work. The agent which they found to be most satisfactory for the production of diffuse growth was Tween 80 (polyoxyethylene derivative of sorbitan mono-oleate) a non-ionic surface active compound obtained from the Atlas Products Co. of Wilmington, Delaware. It was found that, while Tween 80 induced rapid and diffuse growth of the tubercle bacillus, there was

present in the commercial preparations an amount of unesterified oleic acid sufficient to exert a growth-inhibitory effect. This could be removed chemically from the commercial product (22) or counteracted by the addition of serum albumin to the medium.

Dubos and co-workers (21, 23, 24, 25), after extensive investigations on the composition of media containing Tween 80 and serum albumin, have recommended certain basic formulae. Sattler and Youmans (26), using both a modified Proskauer and Beek synthetic medium and the basic medium of Dubos, have studied the effect on growth of the H37 Rv strain of the addition of Tween 80 and serum albumin to the medium. These investigators found that Tween 80, either purified or unpurified, had an inhibitory effect on growth. When 0.2 per cent serum albumin was added, there was no inhibition for the first five days but thereafter a decrease in growth was noted in the media containing Tween 80. Growth in the modified Proskauer and Beek medium appeared to be somewhat better than in the Dubos basic medium.

In this laboratory no extensive study of the relative merits of various media has been made. However, a comparison was made of Kirchner, Proskauer and Beck, and Long's synthetic media for the support of surface growth of *M. tuberculosis*. Blake bottles containing the three media were inoculated by loop transfer with the H37 Rv and Ravenel strains grown on the surface of Kirchner's medium. Growth of the H37 Rv strain was equally rapid on the Kirchner and Proskauer and Beck media but was slower on Long's medium. At a time when the surface of the two former media was entirely covered by growth, only slight spread had occurred on Long's medium. Growth of the Ravenel strain was more rapid on Kirchner's medium than on the Proskauer and Beck and was very slow on Long's medium.

A conference with Dr. Dubos at this time revealed that he also had found Long's medium less satisfactory than one of his own devising which was much like the Kirchner medium in composition.

A comparison of the growth of 2 human strains of *M. tuberculosis* (H37 Rv and R) and 2 bovine strains (Ravenel and D4) was made in the following media: Kirchner's medium, with and without glycerine, containing 0.05 per cent Tween 80 with 0.05, 0.1, and 0.2 per cent human serum albumin, and Dubos (21) Tween 80 serum albumin medium with asparagine, and the same with enzymatic hydrolysate of casein. The various media were distributed in 150 by 18 mm Pyrex glass tubes in 5 ml amounts. Cultures for seeding, which were grown in Kirchner-Tween 80 serum albumin medium, were added to the various media to make final concentrations of 1:400, 1:800, 1:1,600, 1:3,200, 1:6,400, and 1:12,800. The tubes which were incubated at 37°C were observed at two day intervals and the degree of turbidity noted.

The rapidity of growth of the 4 strains in decreasing order was H37 Rv, R, Ravenel, and D4. The human strains grew equally well in all media. Growth of the Ravenel strain was inhibited or retarded in the Kirchner medium containing the least amount (0.05 per cent) of serum albumin, an amount probably insufficient to neutralize the free oleic acid present in the Tween 80. Growth occurred equally well in all other media. The presence of glycerine in the Kirchner medium exerted a retarding effect on the growth of the D4 strain.

*Experiments in vivo* The comparative virulence for mice of the H37 Rv and Ravenel strains, when grown both as a pellicle on the surface of Kirchner's

medium and diffusely in the same medium containing 0.05 per cent Tween 80 and 0.1 per cent human serum albumin, was tested in one experiment

Suspensions of cultures grown for seventeen days on the surface of Kirchner's medium were prepared as follows. The cultures were drained free of fluid on sterile filter paper, removed from the paper, weighed, ground in a Ten Broeck Pyrex glass tissue grinder, and suspended in normal saline in a concentration of 0.1 mg per ml. The cultures which were grown in a medium containing Tween 80 and serum albumin were transferred four times in the medium before use in the virulence test in mice. The cultures were diluted to a turbidity corresponding to that of the 0.1 mg per ml suspensions. As in general, the H37 Rv strain grew more luxuriantly than the Ravenel, the former was diluted 1:20 and the latter 1:10. All cultures, properly diluted, were injected intravenously in 0.5 ml amounts into groups of 10 mice each.

It is realized that turbidity determinations give only a crude estimate of dosage. Therefore, as a further means of estimating the uniformity of the cultures, they were diluted and plated on the surface of Loewenstein's medium for colony count. In later work, in which cultures were plated on both Loewenstein's medium and on Kirchner's agar containing Tween 80 and serum albumin, it was found that higher counts were obtained on the Kirchner agar medium. In neither case, however, can it be assumed that the count represents the actual number of organisms viable and infective for the mouse.

In table 1 the results of this experiment on the comparative virulence of surface and diffusely grown cultures are given. From the limited data obtained, it would appear that diffusely grown cultures are at least as virulent for the mouse as those grown on the surface in the traditional manner. This is in confirmation of the work of Dubos and co-workers (23, 27) who have amply demonstrated the virulence of cultures grown diffusely. Because of the demonstrated virulence of diffusely grown cultures and the fact that they yield more rapid growth and are easier and safer to handle and to standardize, this type of culture was used in all further work.

In three different experiments comparison was made of the virulence of the Ravenel culture grown in Kirchner's medium containing 0.05 per cent Tween 80 and 0.1 per cent human serum albumin and in Dubos basal Tween-albumin medium (24). Groups of 10 mice each received intravenous injection of the two cultures standardized to the same turbidity. The dose used (except one culture) was 0.5 ml of a 1:10 dilution or 0.05 ml of undiluted culture. In the first experiment, growth of the culture in Dubos medium was heavier than in the Kirchner-Tween serum albumin medium. Consequently, the former culture was diluted 1:15 in order that the cultures as injected should have the same turbidity.

The culture grown in the Kirchner-Tween 80 serum albumin medium proved to be the more virulent. As evidence to be presented later will show, the Ravenel culture contains organisms differing in degree of virulence. It is possible that the Dubos medium might favor the growth of the organisms of lesser virulence. The results are given in table 2.

Since experiments *in vitro* had shown that Kirchner's medium, containing 0.05 per cent Tween 80 and 0.1 per cent human serum albumin, satisfactorily supported growth of cultures of *M. tuberculosis*, and experiments *in vivo* had demonstrated that cultures grown in this medium were virulent for mice, it was adopted as the standard medium.

### Choice of Strain of *M. tuberculosis*

Since the comparative avirulence for mice of avian strains of *M. tuberculosis* has been amply demonstrated (12,13,14), only the 2 human and the 2 bovine strains discussed above were studied for virulence.

TABLE 1

Comparison of Virulence of Surface and Diffuse Growth of the H37 R<sub>1</sub> and Ravenel Strains of *M. tuberculosis*

STRAIN	TYPE OF GROWTH	NUMBER OF MICE	DOSE IN TRAPE NO. 5	NUMBER ORGAN- ISMS INJECTED	T <sub>50</sub>
H37 R <sub>1</sub>	Surface	10	0.05 mg	186,000	34
H37 R <sub>1</sub>	Diffuse	10	0.025 ml	407,500	25
Ravenel	Surface	10	0.05 mg	200,000	22
Ravenel	Diffuse	10	0.05 ml	150,000	18.2

TABLE 2

Comparison of Virulence of *M. tuberculosis* Ravenel Grown in Kirchner-Tween 80 Medium and in Dubos-Tween 80 Medium

EXPERI- MENT	CULTURE GROWN IN KIRCHNER MEDIUM				CULTURE GROWN IN DUBOS MEDIUM			
	Number of mice	Dose	Number organisms injected*	T <sub>50</sub>	Number of mice	Dose	Number organisms injected*	T <sub>50</sub>
		ml				ml		
1	10	0.05	1,200,000	21.8	10	0.033	1,600,000	34
2	10	0.05		18.0	10	0.05		24
3	10	0.05	400,000	19.0	10	0.05	550,000	23

\* These figures were obtained from colony counts made from platings on Loewenstein's medium. The cultures in experiment 2 were not plated.

Cultures to be used for mouse injection were grown for five days at 37°C in Kirchner's medium containing 0.05 per cent Tween 80 and 0.1 per cent human serum albumin. The cultures, diluted 1:10 in saline, were injected intravenously in 0.5 ml amount into CF1 albino mice weighing between 16 and 20 Gm. The dose, in terms of undiluted culture, was thus 0.05 ml. The numbers of mice infected with the different cultures were: Ravenel, 150; H37 R<sub>1</sub>, 106; D<sub>4</sub>, 30; and R, 31.

The cumulative rates of death produced by the 4 cultures plotted on arithmetic-probability paper are shown in figure 1.

When the cultures are compared at the time of 50 per cent mortality, they can be arranged in decreasing order of virulence as follows: Ravenel, D<sub>4</sub>,

H37 Rv, and R This represents a difference in time of death between the first and second and the second and third cultures each of only about  $1\frac{1}{2}$  days and between the last two of about 13 days The R strain was thus shown to be much less virulent than the other three strains When the Ravenel, H37 Rv, and D4 cultures are compared at the time of 80 per cent mortality, the greater virulence of the Ravenel culture becomes more apparent At this time, the cultures arranged in decreasing order of virulence are Ravenel, H37 Rv, and D4, with approximately 5 and 8 days difference respectively between the Ravenel and the two cultures of lesser virulence, H37 Rv and D4

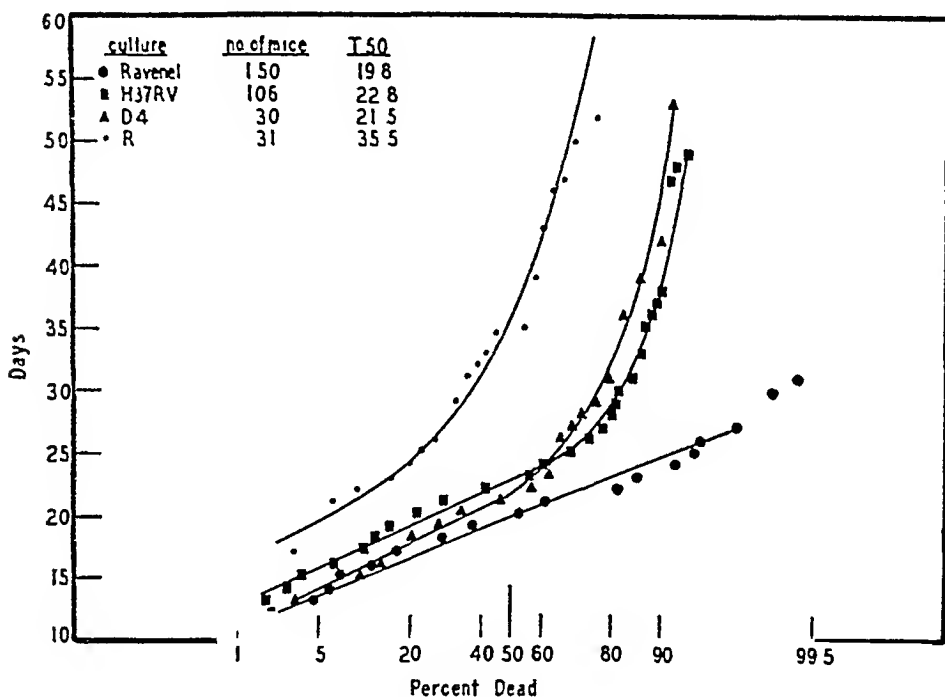


FIG 1 Rates of death of mice infected with four strains of *M. tuberculosis* at a constant dose

It is important in therapeutic tests that all control animals die regularly within a comparatively short space of time The Ravenel culture best fulfills this requirement since it is rare for any mouse to survive beyond a 35 day period following infection with this strain With the H37 Rv, D4, and R strains, 12, 20, and 45 per cent, respectively, of the mice survived beyond this period

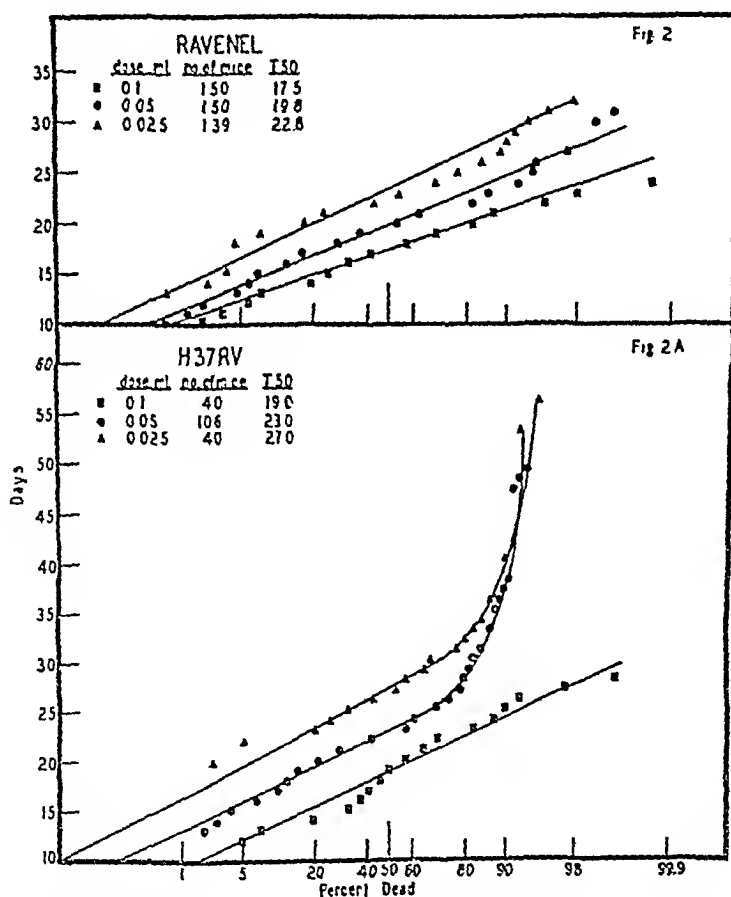
Since there might be some advantage in using a human strain and particularly one which has been used as widely as the H37 Rv, further experiments with this and the Ravenel strain were carried out In these experiments two additional dose levels were used, that is, doses two and one-half times that previously used All injections were given intravenously, the cultures being diluted so that the required dose was contained in 0.5 ml The three doses, in terms of undiluted



culture, were 0.1, 0.05, and 0.025 ml. The numbers of mice infected with each dose of culture were as shown below.

DOSE OF CULTURE ml	NUMBER OF MICE	
	Ravenel	H37 Rv
0.1	150	40
0.05	150	106
0.025	139	40

The per cent mortality on days 10 to 60 after infection is shown in figure 2. In this limited experience the 0.1 ml dose of H37 Rv appears to be comparable



FIGS 2 and 2A Rates of death of mice infected with two strains of *M. tuberculosis* at three different dose levels

to the 0.05 ml dose of Ravenel and might be satisfactory for therapeutic experiments since all mice were dead before 30 days. Another factor, however,

must be considered. Since the 0.05 and 0.025 ml doses of H37 Rv gave 12 and 15 per cent survivors, respectively, at 36 days there is little margin of safety if slight variation in virulence of culture should occur. With both the 0.05 and 0.025 ml doses of Ravenel, the number of survivors was negligible.

The Ravenel strain was thus chosen tentatively as the standard culture for therapeutic studies. It was planned that this selection would be reviewed at a later date when actual therapeutic studies were run with drugs of known antituberculous activity in man (2).

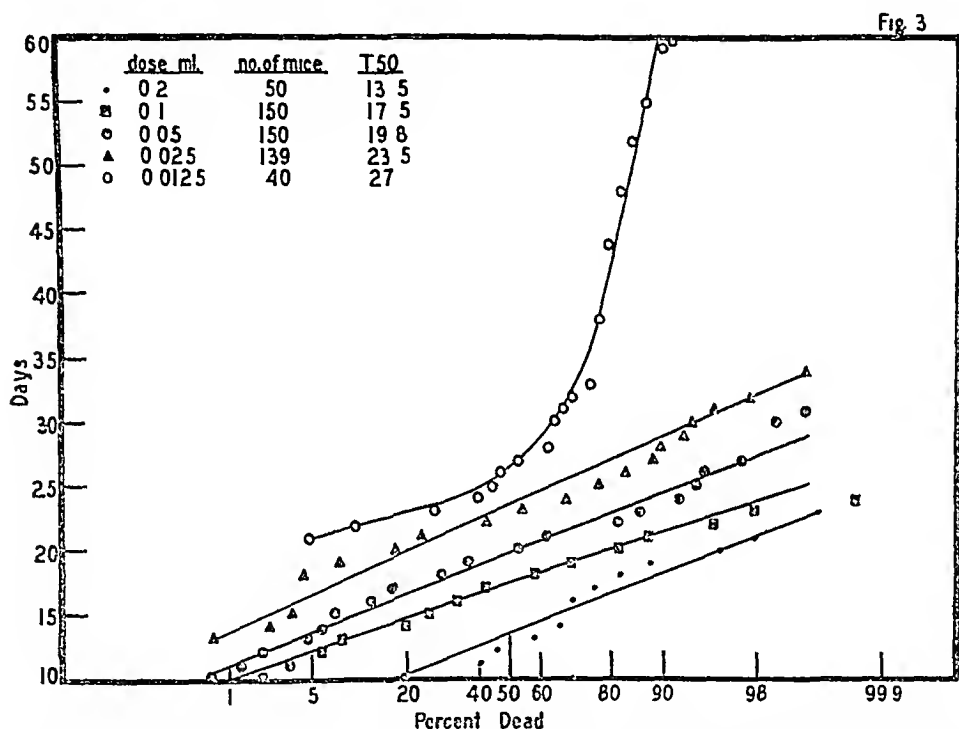


FIG 3 Rates of death of mice infected with the Ravenel strain of *M. tuberculosis* at five different dose levels

#### *Standardization of Dose*

The essential features of a standard dose are death of all control mice within a given time and uniformity of results in different experiments. Five different doses of the Ravenel culture have been studied. The results with doses of 0.1, 0.05, and 0.025 ml have been presented in figure 2. These results with those of two additional doses, 0.2 and 0.0125 ml are presented in figure 3. The numbers of mice in these two latter groups were 50 and 40, respectively.

Twenty-five per cent of the mice receiving 0.0125 ml of the Ravenel culture survived beyond the 35th day, while with the other four doses either none or less than one per cent survived. The results obtained with 0.0125 ml of the Ravenel culture are similar to those obtained with larger doses of cultures of lesser virulence. Since doses of 0.025 and 0.05 ml both gave greater than 99

per cent mortality at 35 days, it was believed that the latter dose would give constant results even if slight variation in virulence of the culture should occur. A dose of 0.05 ml (0.5 ml of a 1:10 dilution) was consequently adopted as the standard for use in therapeutic experiments.

### *Saline vs Egg Yolk as a Suspending Medium for Cultures*

In the experiments which have been described, saline was used as the diluent for all cultures. Pierce, Dubos, and Middlebrook (27) have found that cultures of *M. tuberculosis* possess greater virulence for mice when 25 per cent egg yolk is used as a suspending medium.

Tests were made of the virulence for mice of *M. tuberculosis* Ravenel at five different dose levels when diluted in saline and in saline containing 25 per cent egg yolk. A 50 per cent egg yolk suspension was prepared and mixed with an equal volume of culture suitably diluted to give the final concentration desired.

TABLE 3

*Enhanced Virulence for mice of M. tuberculosis Ravenel When Diluted in Saline Containing 25 per cent Egg Yolk.*

DOSE CULTURE	SALINE SUSPENSION		EGG YOLK SUSPENSION	
	Number mice	T <sub>50</sub>	Number mice	T <sub>50</sub>
0.2	10	14.6	10	10.8
0.1	10	15.8	10	12.5
0.05	32	18.5	30	16.2
0.025	10	22.4	10	18.0
0.0125	10	25.6	10	22.4

The diluted cultures were injected intravenously into mice in 0.5 ml amounts. Ten mice were used for each dose except the 0.05 ml dose in which case 32 mice received the saline suspension and 30 mice the egg yolk suspension.

The  $t_{50}$ 's for the 10 groups of mice may be seen in table 3.

With all doses of culture, the  $t_{50}$ 's for mice injected with the egg yolk suspensions were approximately 2½ to 4 days less than for those injected with saline suspensions. The time interval between first and last deaths was approximately the same for the groups injected with saline and egg yolk suspensions. Since the use of egg yolk rendered both the preparation of inoculum and the injection more difficult, however, it seemed better to adhere to the use of saline suspensions and achieve the desired survival time by control of dosage.

### *Maintenance of Virulence*

*Storage of culture at 5°C* As is frequently the case with cultures of other organisms, it was found that continuous serial transfer resulted in decrease in virulence, while cultures stored in the same medium at 3°C for periods as long as eight to ten months retained virulence.

Weekly serial transfers of a culture were made during a four month period. During two months the virulence remained unchanged but during the third and fourth months it gradually declined. At the end of four months the culture used to initiate the series, which had been stored at 3°C, was transferred to fresh medium and the virulence of the stored culture compared with that of the continuously transferred culture. Serial transfers from the stored culture were then continued for five months when its virulence also declined. These data are presented in table 4.

It is thus possible to maintain virulence in cultures stored in Kirchner-Tween 80 serum albumin medium at 3°C.

It was found that cultures stored at 3°C for long periods of time grew slowly when transferred to fresh liquid medium. In order to determine what reduction in viable organisms occurred during long storage, serial dilutions of a culture stored for ten months were plated on Kirchner's agar containing 0.02 per cent Tween 80 and 0.25 per cent serum albumin. The counts indicated 430,000

TABLE 4

*Comparison of Virulence of M. tuberculosis Ravenel When Continuously Transferred and When Stored at 3°C*

	CONTINUOUSLY TRANSFERRED JUNE 4 TO DECEMBER 31		STORED JUNE 4 TO OCTOBER 4 CONTINUOUSLY TRANSFERRED OCTOBER 4 TO FEBRUARY	
	Number mice	T <sub>10</sub>	Number mice	T <sub>10</sub>
June-July	130	19.3	Stored	
August-September	110	22.6	Stored	
October-December	100	25.4	120	19.4
January	Discontinued		60	19.5
February			30	26.3

viable organisms per ml while fresh virulent cultures plated in this manner give an average count of 17 by 10<sup>6</sup> viable organisms per ml.

It was further found that large inocula of old cultures sometimes failed to initiate growth in fresh media but that growth followed the use of smaller inocula. This inability of a large inoculum to produce growth is illustrated in the following experiment. Ten-fold serial dilutions of three cultures, stored for one year, six months, and two weeks respectively, were made in a series of 5 tubes containing 5 ml of Kirchner-Tween albumin medium. The tubes were incubated at 37°C. Turbidity readings were made at two to three day intervals. Growth did not occur in the 10<sup>-1</sup> dilution of the culture stored for one year but did occur in dilutions 10<sup>-2</sup> to 10<sup>-5</sup>. The cultures stored for six months and two weeks grew in normal fashion, that is, tubes containing the larger inocula grew more quickly than those containing smaller inocula. The rapidity of growth of the three cultures was inversely proportional to the length of storage. The results are given in table 5.

A culture given a ten minute supersonic exposure showed the same inability

to grow in fresh medium when large inocula were used. It was further found that supersonic treatment of the Kirchner-Tween serum albumin medium rendered it incapable of supporting growth when inoculated with a culture of *M. tuberculosis*. It seems probable that slow hydrolysis of Tween 80 during a long period of storage at 3°C, or rapid hydrolysis due to supersonic treatment, releases enough free oleic acid to inhibit growth in fresh medium when large inocula are used.

*Passage of culture through mice* Pierce, Dubos, and Middlebrook (27) maintain the virulence of cultures of *M. tuberculosis* by passage through mice. They readily obtained virulent cultures from lung, heart, or spleen tissue by cultivation in liquid medium.

TABLE 5

*Growth of Three Cultures of M. tuberculosis Ravenel after Storage for One Year, Six Months, and Two Weeks*

TUR BID- ITY	CULTURE-TIME OF STORAGE														
	One year					Six months					Two weeks				
	Culture dilution														
	10 <sup>-1</sup>	10 <sup>-2</sup>	10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-5</sup>	10 <sup>-1</sup>	10 <sup>-2</sup>	10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-5</sup>	10 <sup>-1</sup>	10 <sup>-2</sup>	10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-5</sup>
dc <sub>3</sub> s															
2	Tr*	-	-	-	-	Tr	-	-	-	-	+	+ -	-	-	-
4	Tr	-	-	-	-	2+	+ -	-	-	-	2+	+	+ -	-	-
7	Tr	-	-	-	-	4+	3+	+	-	-	4+	1+	2+	+	-
10	Tr	-	-	-	-	4+	4+	2+	-	-	4+	4+	3+	2+	+ -
13	Tr	+	+ -	-	-	4+	4+	3+	+	+ -	1+	4+	3+	3+	2+
16	Tr	2+	2+	+	-	4+	4+	3+	2+	2+	4+	4+	1+	3+	3+
19	Tr	4+	4+	3+	+	4+	4+	4+	4+	3+	4+	4+	4+	4+	4+

\* Tr (trace) in the 10<sup>-1</sup> dilution of cultures indicates turbidity due to amount of original culture present and not to growth.

Blood and tissue suspensions of mice infected with *M. tuberculosis* Ravenel were cultured on Loewenstein's medium, and were inoculated into Kirchner's medium, and Kirchner's containing Tween 80 and serum albumin. Difficulty was found in obtaining positive cultures in the medium containing Tween 80. This was found to result from the fact that mouse serum and tissue contain a lipase which hydrolyzes Tween 80 with the production of free acid inhibitory to the growth of the tubercle bacillus. In a further study of the sera of normal animals, it was found that guinea pig and mouse sera were equally potent in hydrolyzing Tween 80. Rabbit serum also contained lipase but to a lesser degree. Davis and Dubos (25) have shown that horse serum also contains a lipase capable of hydrolyzing Tween 80. Positive cultures were obtained, however, in Kirchner's medium and on Loewenstein. Transfers from these media were made to Kirchner-Tween 80 serum albumin medium for virulence test. Eight cultures obtained from the blood or organs of 3 different mice have been so tested. In table 6 is shown the high virulence of all of these cultures.

When serial passage in mice was tried, it appeared that the virulence increased through four passages. The fifth passage, however, proved to have about the same virulence as the first. Passages were not made directly from mouse to mouse by use of tissue suspensions but by infecting each mouse in series with cultures grown on artificial medium obtained from the previous mouse. Brown-ing and Gulbransen (11) tested the effect on virulence of direct passage from mouse to mouse. They used 8 strains with 3 to 8 passages each and concluded that, while virulence repeatedly appeared to increase, there was no maintenance of such increase.

It thus appeared that results obtained by mouse passage were not sufficiently uniform to render advisable the use of this method for maintenance of virulence.

*Employment of cultures derived from rough colonies.* Dubos, Davis, Middlebrook, and Pierce (23) and Middlebrook, Dubos, and Pierce (28) have described

TABLE 6  
*Virulence of Culture of M. tuberculosis Ravenel Recovered from Infected Mice*

CULTURE RECOVERED FROM		DOSE	NUMBER MICE	T <sub>50</sub>
Mouse	Tissue			
1	Blood	ml 0.05	20	18.8
2	Heart	0.05	10	18.8
	Lung	0.05	20	17.4
	Spleen	0.05	10	15.4
3	Blood	0.05	20	17.6
	Heart	0.05	10	14.8
	Spleen	0.05	10	19.0
	Lung	0.05	20	16.4

the growth of virulent and avirulent cultures of *M. tuberculosis* on the surface of a Tween albumin agar medium. In order to get satisfactory growth, they found it necessary to use a 0.5 per cent concentration of serum albumin. On this medium colonies developed within seven to fifteen days. They found that the type of colony of both virulent and avirulent bacilli changed from rough to smooth as the concentration of Tween 80 in the medium was increased. Virulent bacilli, however, retained their rough characteristics in higher concentrations of Tween than did the avirulent bacilli.

This method of colony differentiation into virulent and avirulent types appeared to offer an excellent opportunity to obtain highly virulent cultures derived from single rough colonies. Using Kirchner's medium as a base with the addition of 1.5 per cent washed agar, Tween 80 was added in 0.005, 0.01, 0.02, and 0.05 per cent. To this agar containing each concentration of Tween 80, bovine serum albumin, fraction V, was added in 0.1, 0.2, and 0.5 per cent and plates were poured. The plates were inoculated with 0.1 ml of  $10^{-4}$  and  $10^{-5}$

dilutions of *M. tuberculosis* Ravenel grown in Kirchner-Tween 80 serum albumin medium. The inoculum was allowed to spread by gently tilting the plates which were then sealed with cellulose tape and incubated at 37°C.

In confirmation of Dubos' results, predominantly rough colonies appeared on the plates containing 0.005 and 0.01 per cent Tween 80 and an increasing proportion of smooth colonies on the agar containing 0.02 and 0.05 per cent Tween

TABLE 7

*Comparative Virulence of Cultures Derived from Smooth and Rough Colonies of M. tuberculosis Ravenel*

CULTURE	COLONY TYPE	DOSE	COLONY COUNT MILLIO /ML	NUMBER MICE	T <sub>50</sub>	
1	Rough	0.05	not made	10	17.3	
	Smooth	0.05	not made	10	37.0	
2	Rough	0.05	16.5	20	18.6	
	Smooth	0.05	70.0	18		11 died 23 to 76 days 7 killed 86th day
3	Rough	0.05	9.0	20	20.1	
	Smooth	0.05	39.7	10		3 died 50 to 160 days 7 killed 160th day
4	Rough	0.05	not made	10	20.0	
	Smooth	0.05	not made	10		5 died 35 to 81 days 5 killed 129th day
5	Rough 1	0.05	6.0	10	20.2	
	Rough 2	0.06	not made	10	17.8	
	Smooth 1	0.05	93.0	10		6 died 17 to 108 days 4 killed 122nd day 10 killed 121st day
	Smooth 2	0.05	not made	10		
6	Rough 1	0.05	7.0	10	20.0	
	Rough 2	0.05	7.5	10	20.0	
	Smooth 1	0.05	54.5	10		8 died 26 to 72 days 2 killed 122nd day 3 died 69 to 108 days 7 killed 122nd day
	Smooth 2	0.05	75.0	10		

80. The concentration of serum albumin appeared to have little influence on colony type. With 0.05 per cent Tween 80, however, growth was slightly inhibited in the presence of 0.1 per cent but not in the presence of 0.2 and 0.5 per cent serum albumin.

In later work, Kirchner agar containing 0.02 per cent Tween 80 and 0.25 per cent bovine serum albumin was used. On this agar colonies appear as rough, intermediate, or smooth. The rough colonies are flat and spreading, have a small dense center and a delicate lacy border. The smooth colonies are denser

and more uniform in appearance, with a glistening surface and a well defined edge

Both rough and smooth colonies have been picked from 6 different Ravenel cultures, plated on Kirchner's agar containing 0.02 per cent Tween 80 and 0.25 per cent bovine serum albumin. These colonies were transferred to Kirchner-Tween 80 serum albumin fluid medium and, when heavy growth occurred (usually in about seven days), transfers were made to fresh medium in the usual manner. After incubation for five days, the cultures were tested for virulence. In table 7 the high virulence for mice of the rough colony cultures in contrast to the very low virulence of the smooth colony cultures is shown.

From these experiments, it is clear that virulence is associated with the rough colony type which develops when the cultures are grown on agar containing 0.02 per cent Tween 80 and 0.25 per cent serum albumin.

In a further study, 21 cultures derived from rough colonies have been tested for virulence. Seventeen out of the 21 cultures gave  $t_{50}$ 's varying between 17.6 and 21.6 days with an average of 19.7 days, while the  $t_{50}$ 's of the 4 cultures of lesser virulence varied between 23 and 25 days. Twenty-six virulent cultures, transfers from the original culture and maintained in Kirchner-Tween 80 serum albumin medium at 3°C, gave  $t_{50}$ 's varying between 16.8 and 21.6 days with an average of 19.7 days.

The above cultures, at the time virulence tests were made, were all plated in order to study the correlation between virulence and proportion of rough and smooth colonies. The results have been disappointing. Colony differentiation was not always clear-cut, and unexplained differences occurred in colony form on duplicate plates made from the same culture. Studies are now in progress to develop a technique by which more consistent results can be obtained.

#### *Standard Procedure for Maintaining Cultures of M. tuberculosis Ravenel for Mouse Infection*

For the purpose of obtaining rough colony cultures to be used for mouse infection, a virulent culture of *M. tuberculosis* Ravenel is plated on Kirchner's agar containing 0.02 per cent Tween 80 and 0.25 per cent bovine serum albumin, fraction V. (A 5 per cent serum albumin solution made in distilled water and sterilized by filtration is added to the melted agar which has been cooled to 56°C.) Four to six plates containing 15 ml. of the above agar are inoculated with 0.1 ml. of a  $10^{-4}$  dilution of culture. The inoculum is placed on the surface of the agar and allowed to spread by gently tilting the plates which are then sealed with cellulose tape and incubated at 37°C for twenty-one days. Fresh cultures are started from rough colonies picked from these plates and such cultures, after two transfers in Kirchner-Tween serum albumin medium, are injected into mice and stored at 3°C. If found to be of satisfactory virulence they are available for use as seed cultures.

The cultures to be used for mouse infection in the actual tests are inoculated with the seed cultures obtained as described above. These cultures, which are grown in 50 ml. Erlenmeyer flasks containing 20 ml. of Kirchner's medium with



0.05 per cent Tween 80 and 0.1 per cent human serum albumin, are started by an inoculum of 2 ml of the virulent, stored culture, and incubated for five days at 37°C. As a check on purity of the culture, a transfer is made after two days' incubation to beef heart broth. In this medium the tubercle bacillus does not grow but the usual contaminants grow well. As a further check on the purity of the culture, an aliquot is examined by the Ziehl-Neelsen method just before use. Turbidity of the culture is then determined by comparison with McFarland (29) nephelometer tubes. With a standard procedure for maintaining cultures, the turbidity of the virulent Ravenel culture is fairly constant. It has been observed, however, that, when cultures lose virulence, growth becomes heavier. The organisms of lesser virulence evidently reproduce more rapidly under the standard conditions described. If found to be of standard turbidity, the culture is diluted 1:10 with saline and injected intravenously in 0.5 ml amounts.

#### SUMMARY

A procedure for maintaining cultures of *M. tuberculosis* of standard virulence for use in therapeutic experiments in mice has been established.

The standard medium chosen for growth of cultures was Kirchner synthetic medium with the addition of 0.05 per cent Tween 80 and 0.1 per cent human serum albumin.

A bovine strain of *M. tuberculosis*, the well-known Ravenel, was chosen as the standard strain since it proved more virulent and gave more constant results than three other strains tested.

The Ravenel culture when maintained in this medium under the conditions described retains its virulence for mice and gives uniform results in successive experiments. A five day culture when diluted 1:10 with saline and injected intravenously in 0.5 ml amount gives greater than 99 per cent deaths within 35 days with an average  $t_{50}$  of 19.8 days.

#### SUMARIO

*Empleo del Ratón en una Prueba Normalizada de la Actividad Antituberculosa de los Compuestos de Origen Sintético Natural. I. Selección y Normalización del Cultivo*

Queda establecido un procedimiento para mantener cultivos del *M. tuberculosis* de virulencia tipo para empleo en los experimentos terapéuticos en ratones.

El medio tipo escogido para los cultivos fué el sintético de Kirchner con la adición de 0.05 por ciento de "Tween 80" y 0.1 por ciento de seroalbúmina humana.

Como cepa tipo se tomó una cepa bovina del *M. tuberculosis*, la conocida Ravenel, por resultar más virulenta y dar resultados más constantes que otras tres cepas comprobadas.

El cultivo Ravenel, mantenido en dicho medio en las condiciones descritas, retiene su virulencia para los ratones y rinde resultados uniformes en experi-

mentos sucesivos. Un cultivo de cinco días, diluido al 1:10 con solución salina e inyectado intravenosamente en cantidades de 0.5 ml, provoca más de 99 por ciento de muertes en término de 35 días con un promedio de  $t_{50}$  de 19.8 días.

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# THE USE OF THE MOUSE IN A STANDARDIZED TEST FOR ANTITUBERCULOUS ACTIVITY OF COMPOUNDS OF NATURAL OR SYNTHETIC ORIGIN<sup>1</sup>

## II Choice of Mouse Strain

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### INTRODUCTION

Despite its widespread use in the study of chemotherapy of many experimental diseases, the mouse has been extensively used for therapeutic evaluations in experimental tuberculosis only in relatively recent years. Hesitancy over use of this animal arose for several reasons, the chief one of which was the impression that this species was highly resistant to infection. Undoubtedly this belief grew up from work done early in this century in which the intraperitoneal or subcutaneous routes of inoculation were employed. Much of this early work has recently been reviewed by Raleigh and Youmans (1a) and detailed reference to it need not be made here, except perhaps to put additional emphasis on differences in various mouse strains in their susceptibility to experimental infection with this agent.

Koch (2) reported the very early observation that field mice (*Arvicola arvalis*) were more susceptible than house mice. Although studies employing various strains of the house mouse (*Mus musculus*) have been described during the ensuing years, little has been said about strain differences in susceptibility. This problem was attacked recently by Pierce, Dubos, and Middlebrook (3). Their work was facilitated by the improved cultures obtained by the use of a dispersing agent (Tween) in their culture medium. Of 22 strains of mice of varying degrees of homozygosity from various sources which they tested, they listed 18 in the following order of increasing susceptibility to tuberculous infection: Swiss albino (4 strains from different sources), Swiss albino CFW, Swiss albino CFCW, Strong A, Strong C, Buffalo, Rockefeller Institute strain, Chocolate, Brown spot, C<sub>3</sub>H (strains from two sources), Strong I, *Mus musculus* domesticus (raised in Rockefeller Institute), C<sub>67</sub> black, and dba (line 1). Thus in general, pigmented animals were found to be more susceptible than albino strains.

During the past few years similar studies have been carried out in this laboratory. One point of especial emphasis has been to seek a strain of mouse with not only high susceptibility but also with as uniform a response as it was possible to find. Such characteristics would help greatly to evaluate various compounds

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of possible therapeutic value. It was recognized at the outset that the most susceptible strains might not necessarily be the most uniform in response.

Martin (4) presented an analysis of his data on the rate of death of mice following a fixed intravenous inoculation, but it is not clear as to what type or strain of mouse he used. Deaths occurred between the fifteenth and thirty-first days following inoculation, with a peak of deaths occurring on the nineteenth and twentieth days, and with approximately 5 per cent surviving through the thirty-first day. In two experiments described by Youmans and McCarter (5) 40 per cent of the control mice survived through the twenty-eighth day in one case, while only 13 per cent survived this period in the second. In both experiments the earliest deaths occurred on the seventeenth or eighteenth day. These authors described their mice as being white Swiss of about 25 Gm weight. In later work, Youmans and Raleigh (1b, c) employed the Strong A strain of albino mice averaging 6 to 8 weeks in age, usually weighing between 20 and 25 Gm. The inoculum consisted of 0.1 mg of *M. tuberculosis*. The rate at which the mice died following inoculation was not reported but apparently there was considerable variation, since survival times ranging from 14 to as long as 94 days were mentioned with an average of about 25 days (1b). Probable reasons given for the differences were variations in the inoculating culture as well as in individual resistance of mice. On the latter score it may be noted that Pierce, Dubos, and Middlebrook (3) listed the Strong A strain of mice as amongst the more resistant tested.

Raleigh and Youmans (1b) mentioned also the possibility that development of bacterial hypersensitivity may play a role in variations. According to Martin (4), mice receiving a small inoculum may show marked increases in survival time "due to the rapid development of a measure of resistance."

#### EXPERIMENTAL

The prime purpose of the work to be described here was to find a strain of mice giving the most uniform response possible. Relatively short survival time was the second consideration. The standardization of inoculum for these tests was described in a previous paper (6) and for the reasons there given the Ravenel strain of *M. tuberculosis* var. *bovis* has been employed throughout.

Preliminary studies were carried out with 7 strains of mice, as follows: CF1 (Carworth Farms albino with brown, non-agouti background), CFW (Carworth Farms albino, agouti), Rockefeller (Princeton) albino, Tumblebrook (Swiss Webster), CFCW (CFW mutant), dba (line 1), and C<sub>57</sub> black, sub-line 6 (the latter two are inbred strains from the Jackson Memorial Laboratory, Bar Harbor, Maine). The C<sub>57</sub> strain is black, non-agouti, and the dba is a dilute brown, non-agouti.)

The Ravenel strain of *M. tuberculosis* grown in a modified Kirchner's medium containing Tween 80 and serum albumin, under standard conditions as described previously (6), was diluted to a standard turbidity and the mice under study were given an intravenous inoculation of 0.5 ml of the diluted culture. (Usually this consisted of a 1:10 dilution of a five day culture, containing on an average



such graphs deviated significantly from a straight line, with early deaths occurring at rates similar to those of other strains tested, while some mice survived longer than might be expected according to a normal frequency distribution. It is believed that this indicates a lack of homogeneity in response on the part of these strains to experimental infection with *M. tuberculosis*. The remaining 5 strains all died at rates giving straight lines on probability paper indicating that death times followed a normal frequency distribution curve. From these plots it is possible to determine the 50 per cent death times ( $t_{50}$ ). A comparison of the 7 strains of mice on this basis is shown in table 1.

Since these preliminary studies were carried out with groups of only 20 mice each, no particular significance can be put on the exact order in which the  $t_{50}$  values appear. It was somewhat surprising, nevertheless, to find that the  $C_{57}$  blacks apparently were somewhat more resistant than some of the albino strains. It will be recalled that Pierce, Dubos, and Middlebrook (3) had found this strain (sub-line not indicated) to be one of the most susceptible to the H37 Rv strain of *M. tuberculosis*. Unfortunately, the Bar Harbor disaster prevented the fur-

TABLE 1

*Comparison of 50 per cent Death Times ( $t_{50}$ ) of Various Strains of Mice Experimentally Infected with *M. tuberculosis* (Ravenc)*

MOUSE STRAIN	$t_{50}$
	days
CF1	19.6
dba, line 1	20.0
Rockefeller	20.2
CFCW	21.8
CFW	22.3
Tumblebrook	22.4
$C_{57}$ black, sub-line 6	23.0

ther investigation of this point. In recent months it has again become possible to obtain mice of the  $C_{57}$  black strain, sub-line 6, and 40 additional mice (20 mice in each of two tests) were inoculated under standard conditions along with CF1 mice as controls. The results of the more recent duplicate tests agreed with each other very well, but did not agree completely with previous findings. Thus while the CF1 mice gave a composite  $t_{50}$  of 19.7 days (average survival time = 20.2 days), the  $C_{57}$  blacks gave a  $t_{50}$  of 20.7 days (average survival time = 21.7 days) indicating on this score a greater similarity in sensitivity between the two strains than had been found in earlier tests. However, again the CF1 mice showed a greater uniformity in response in that all deaths occurred between the sixteenth and twenty-fifth days following inoculation while in the  $C_{57}$  blacks, deaths spread out from the thirteenth day through the thirty-ninth day.

In general it appeared that the various strains of mice tested fell into two groups. One consisted of animals showing remarkable homogeneity of response to this experimental infection. In this group could be placed the CF1, CFCW,

dba, and C<sub>57</sub> black strains. In the second group, in which the CFW and Tumblebrook strains could be placed, the individual members showed greater variation in response to this infection. It will be noted that such a rough classification would put the CFW mouse in one group, and a mutant of this strain the CFCW in another, but to speculate further at this point would be extremely hazardous. Time-mortality curves of a relatively long term infection such as that with *M. tuberculosis* are undoubtedly the results of the composite effects of many complex factors. It was felt essential, however, that more extensive studies be carried out on much larger groups of mice. For this purpose two strains were chosen, one strain from each of the two groups described. The CF<sub>1</sub> strain, because of ready availability, was picked to exemplify the homogeneous group, while the CFW strain was chosen as an example of the heterogeneous group. Eleven separate tests, employing a total of 149 mice, were

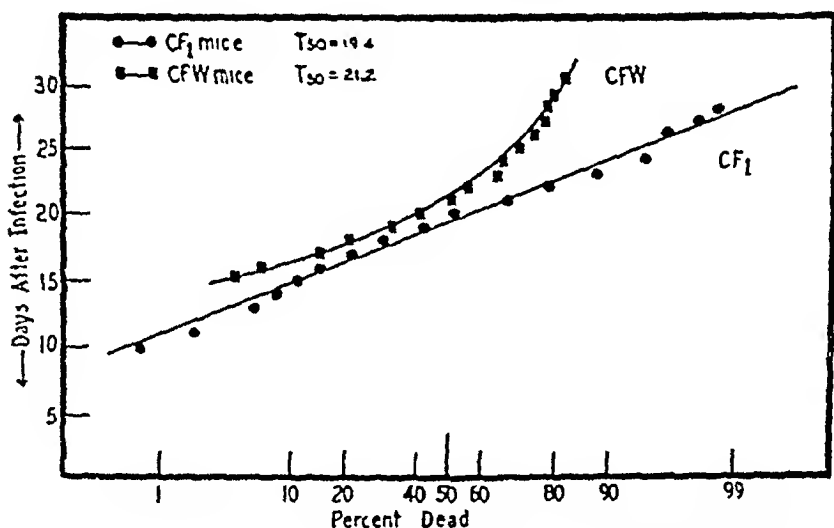


FIG. 4. Rates of death of mice experimentally infected with *M. tuberculosis*

carried out with CF<sub>1</sub> mice, and 14 tests, totaling 139 mice, with the CFW. As before, all mice received a similar, standardized, intravenous inoculation with *M. tuberculosis* (Ravenel).

For the sake of brevity, the composite results of all of these tests are shown graphically in figure 4 which shows the time-mortality curves for the two strains. As had been found in the preliminary studies, experiments with large groups of mice showed that the CF<sub>1</sub> strain was significantly more uniform in response than the CFW to the standard infection with *M. tuberculosis* (Ravenel). Accordingly the CF<sub>1</sub> strain was chosen as the standard mouse to be used in chemotherapeutic studies, a description of which appears in the third paper of this series (7).

#### *The Choice of Route of Inoculation*

Thus far the discussion has been limited to the response of various strains of mice following infection via the intravenous route. Other routes of infection in



mice have been employed in various laboratories. The Royal Commission on Tuberculosis (8) found in its very early work that rats and mice were relatively resistant, especially to small doses, when *M. tuberculosis* was administered intraperitoneally, subcutaneously, or fed in the diet. A number of workers have employed the respiratory route of infection. Glover (9), for example, reported that a dose of about 100 organisms would infect some mice, 1,000 organisms infected nearly all, but the minimal lethal dose was estimated at about 120,000 organisms. Intranasal inoculation gave less consistent results than exposure to an infected mist. Concentrated aerosol mists induced intensive pulmonary consolidation within 60 days. Weaker suspensions were not lethal, but caused discrete, slowly progressive foci. The strain, age, and weight of mice used were not indicated.

Pierce, Dubos, and Middlebrook (3) have studied tuberculosis in mice following inoculation via the intravenous, intraperitoneal, and intracerebral routes. The minimal infective dose was said to be 0.0005 to 0.02 mg. of bacilli by the first route. The second avenue of infection (intraperitoneal) was much less effective, although it could be improved by using as inoculum a culture suspended in egg yolk. In the intracranial route, as few as 10 to 100 bacilli, it was estimated, gave rise to very rapid growth of the organism. It is not possible, however, to make a comparison between the death rates following intravenous and intraperitoneal inoculation since these data are not given for the latter route.

The several routes of inoculation were taken into consideration in the present work. The intranasal inoculation presents undue hazards for the laboratory worker, especially when employed in air-conditioned buildings, and therefore was eliminated on this score.

On the basis of the report of Pierce, *et al.* (3), it would appear that intracerebral inoculation may prove to be a convenient method for detection of *M. tuberculosis* in sputum since very small inocula are detectable by this means. Although pulmonary lesions were noted 3 weeks after infection, it was not clear from the data, as already noted above, at what rate deaths followed inoculation by this route. Since the present studies were designed primarily for chemotherapeutic tests, many of which would involve the use of new, and possibly poorly defined, substances, consideration had also to be given to the question of whether or not any substance under test would pass through the blood-brain barrier following administration parenterally or by mouth. As this type of information would not always be available, it was felt that the intracranial route might lead to undue complications for this purpose. Hence comparisons were made of intraperitoneal (employing yolk fluid as a suspending medium) and intravenous inoculation. The results of typical experiments of this type are shown in table 2.

It is apparent that whether or not egg yolk is used as the diluent, intravenous inoculation leads to considerably more rapid death in mice than does intraperitoneal inoculation even when the inoculum used via the latter route is ten times as large as that used in the former.

It is also evident that the use of egg yolk accelerates the death rate following intravenous inoculation, as compared to inocula prepared in saline. However,

on the basis of results with admittedly small numbers of mice, it appeared that the use of egg yolk for intravenous inoculation did not lead to any more reproducible results than did using saline-suspended inocula. Hence it was decided not to use egg yolk in the routine chemotherapeutic tests to be described in a third paper of the present series (7).

*The Effect of Age, Weight, and Sex of Mice Used in Experimental Tuberculosis Experiments in CF1 Mice*

After the test had been standardized as to strain of *M. tuberculosis* (6), diluting fluid of inoculum, strain of mice, and route of inoculation, attention was turned to the question of the effects of age, weight, and sex of the CF1 mice on the death rate following a fixed inoculation. It is evident that age and weight are some-

TABLE 2

*Comparison of Intravenous and Intraperitoneal Inoculation of CF1 Mice with M. tuberculosis (Ravenc1)*

NUMBER OF MICE	INOCULUM		ROUTE	T <sub>50</sub>	AVERAGE SURVIVAL TIME
	Diluent*	Dose† ml			
42	25 per cent yolk	0.05	IV	16.1	15.3
30	0.9 per cent saline	0.05	IV	19.6	19.9
29	25 per cent yolk	0.5	IP	22.5	24.4
10	25 per cent yolk	0.25	IP	27.5	35.7
10	25 per cent yolk	0.125	IP	35.8	39.1

\* Final concentration of diluting material

† Dose given in terms of undiluted 5 day culture. For intravenous inoculation the dose was diluted to 0.5 ml with the given diluent while for intraperitoneal injection the final volume was 1.0 ml.

what interdependent and there are limitations as to the age limits obtainable within a given weight range. However, as shown in table 3, which summarizes the results of a number of experiments, it can be seen that CF1 mice of either sex, weighing between 14 and 18 Gm. and ranging in age from 4 to 6 weeks all respond in a very similar fashion to the standard intravenous inoculation with *M. tuberculosis* (Ravenc1) as used in the present tests. On the other hand, amongst CF1 mice 10 weeks of age or older, deaths following the standard inoculation occur not only more slowly, but also the rates deviate considerably from a normal frequency distribution curve and hence do not give straight lines on probit paper as described above.

*The Choice of Suitable End Points in Experimental Tuberculosis in the Mouse*

One difficulty which has always been present in studies in experimental tuberculosis in animals has been that of interpretation of results once they have been obtained. Feldman (10) has described a numerical scheme for recording the degree of tuberculous changes occurring in the experimentally infected guinea pigs. In a later paper (11) it was emphasized that one of the chief problems in

the search for chemotherapeutic compounds for tuberculosis was the difficulty in distinguishing definitely between effective and noneffective substances in a test of only short duration

In using the mouse for assessment of therapeutic action of various compounds in tuberculosis, Martin (4) used the increase in the arithmetic mean survival time of treated mice as compared to infected, but untreated, controls. He noted that when more than 5 out of 24 mice survived beyond the end of the experiment (30 days) a better measure of therapeutic efficacy could be obtained by comparison of median survival times, i.e., the times taken for 50 per cent of the animals in the various groups to die. The median survival time was estimated from a smoothed probit-cumulative distribution curve. Although the difference in reliability between the two methods was found to be small, the use of the mean survival time was considered more reliable.

Youmans and Raleigh (1c) employed several criteria for measuring therapeutic

TABLE 3

*Effect of Age, Weight and Sex on Rate of Death of CF1 Mice Following Intravenous Inoculation with M. tuberculosis (Ravencel)*

SEX	AGE WEEKS	AVERAGE INITIAL WEIGHT	NUMBER OF MICE	Time	AVERAGE SURVIVAL TIME
		Gm		Days	Days
♂	4 to 5	16.2	152	20.3	21.0
♀	4 to 5	15.2	153	20.1	20.5
♂	5 to 6	17.7	153	20.0	20.7
♀	5 to 6	16.4	154	19.3	20.3
♂	10 to 12	24.0	29	25.1	28.3
♀	10 to 12	23.2	20	25.0	27.6
♀	6 months	24.8	8	36.0	38.0

action of various compounds in experimental tuberculosis in the mouse. These criteria included average survival time, per cent mortality, weight response, and gross and microscopic tuberculous involvement of the tissues. Apparently, no attempt was made to compose these separate operations into comparative indices or ratios of activity and it is not clear how two drugs would be compared on a relative basis. In discussing Martin's procedure of comparing drug activities solely on the basis of average survival times, these authors expressed the feeling that in experimental tuberculosis in the mouse direct examination of tissues for suppression of lesion development was a "necessary measure of chemotherapeutic action."

In the earlier stages of the work on experimental tuberculosis in the mouse in our laboratory, attempts were made to employ, as one of the criteria, the degree of tuberculous involvement of the various tissues. This will be discussed more fully in the third paper of the present series (7). The present paper will limit itself to a discussion of the death rates of the CF1 mice following the standardized inoculum.

Examination of death rates of CF1 mice infected with standardized *M tuberculosis* (Ravenel) inocula in many replicate tests carried out over several years time indicate that, when these mice receive no therapeutic treatment, the cumulative percentage dead plotted on a probability scale against time in days on an arithmetic scale<sup>3</sup> gives a straight line. This indicates that the death-time relationship follows a normal frequency distribution curve. Using what are apparently somewhat less susceptible mice, Raleigh and Youmans (1b) also observed this type of distribution. It is implied also in the data published by Martin (4). The extent to which such curves deviate from a straight line on probit paper is a measure of the variation from this normal distribution and, as indicated earlier, has been taken to be a measure also of the uniformity of response of a given group or strain of mice. It will be recalled that Bliss (12) calculated time-mortality curves in various biological systems and employed in his graphic analysis plots of survival time on a logarithmic scale against mortality in probits. Furthermore, Bliss computed curves statistically from the same data and showed that using log time the provisional curve (obtained by plotting experimentally observed mortality in probits against log time) agreed closely with the computed curves. Such computations have not been carried out with time-mortality data obtained from studies of experimental tuberculosis in the mouse. As already noted, however, it was found that straight lines are obtained by plotting cumulative per cent dead on a probability scale (which is the equivalent of using probits) against time on an arithmetic scale. Using log time does not appreciably improve the nature of this line nor does it significantly change the estimated  $t_{50}$ . Thus, when the data obtained with CFW mice (figure 4) are plotted, using log time instead of arithmetic time, there is a deviation from a straight line above 65 per cent mortality, although this deviation is less marked since the log time scale condenses the points with increased time.

It should be pointed out, however, that Bliss, in addition, provided a procedure which, though laborious, did permit calculation of the error in estimating the time in which any per cent mortality desired had occurred. Any advantages which may be derived from making comparisons on a basis other than the 50 per cent mortality time are not yet obvious in our present work. Hence the  $t_{50}$  (50 per cent mortality time) has been used as the chief "end point" criterion in these studies.

Early in the work it was decided that it would be of value to compare  $t_{50}$  values (obtained by plotting on arithmetic-probability paper as already described) with average survival times. In table 4 such data from 12 separate experiments are listed. In each case 10 to 20 CF1 mice receiving the standard intravenous inoculum were employed.

It is obvious that, under the experimental conditions employed, the values for the estimated  $t_{50}$ 's and the average survival times coincided very closely. The standard deviation from test to test for the  $t_{50}$  value was 1.97 days, or 10.3

<sup>3</sup> A convenient type of graph paper for this purpose is the arithmetic-probability chart sheet such as that printed by the Codex Book Company of Norwood, Massachusetts, under their catalogue number 3127.

per cent, while for the average survival time it was 1 85 days, or 9 26 per cent. The advantage in using the  $t_{50}$  from a practical standpoint lay in the ability to estimate the  $t_{50}$  before 100 per cent of the mice had died. Also, in those occasions when deaths occurred erratically, it was obvious from the nature of the curve obtained that the test was atypical.

Furthermore, it was anticipated that treatment with therapeutic agents would prolong the lives of some individual mice to a much greater extent than others. One or two mice out of 10 living much longer than the rest could lead to a significantly changed value for the average survival time without appreciably changing the  $t_{50}$ . Hence, as a standard practice  $t_{50}$  values were employed in preference to average survival times.

TABLE 4

*Comparison of  $t_{50}$  and Average Survival Time in CF1 Mice Inoculated with *M. tuberculosis* (Ranel)*

EXPERIMENT NUMBER	$t_{50}$	AVERAGE SURVIVAL TIME
	Days	Days
1	18 2	18 8
2	19 8	19 8
3	18 3	18 7
4	17 7	20 4
5	20 8	21 4
6	17 5	18 5
7	13 7	15 7
8	18 4	18 8
9	20 3	21 0
10	20 8	22 1
11	21 0	22 1
12	21 0	22 3

## SUMMARY

Using a carefully standardized inoculum of *M. tuberculosis* var. bovis (Ranel) grown in a liquid medium containing Tween 80, comparisons have been made of the death rates of 7 strains of mice. The mouse of choice on the basis of uniformity of response, as well as ready availability in large supply, was found to be an albino mouse with brown, non-agouti background, the CF1. Intravenous inoculation was shown to be preferable to the intraperitoneal route even when egg yolk was used as the suspending medium for the inoculum. As was the case with the selection of the Ranel strain of *M. tuberculosis* var. bovis the choice of the mouse was regarded as tentative. Final choice could only be made when results were available on tests in this animal of drugs with known antituberculous activity in man (7). The most uniform results were obtained with CF1 mice weighing between 14 to 18 Gm. and ranging in age from 4 to 6 weeks.

Deaths in CF1 mice of appropriate age receiving a standard intravenous inoculum followed a normal frequency distribution curve which gave straight lines when cumulative percentage mortality, on a probit scale, was plotted against

time on an arithmetic scale. Such straight lines provide a relatively simple procedure for determining the 50 per cent mortality time ( $t_{50}$ ). Among infected CF1 mice receiving no therapeutic treatment, there was little difference between  $t_{50}$  and average survival times. For certain practical considerations, however, the  $t_{50}$  was considered to be preferable to the average survival time as an end point criterion in a test designed for chemotherapeutic studies.

#### SUMARIO

*Empleo del Ratón en una Prueba Normalizada de la Actividad Antituberculosa de los Compuestos de Origen Sintético Natural II Selección de la Cepa Murina*

Tomando un inóculo cuidadosamente normalizado de *M. tuberculosis*, var *bovis* (Ravenel), cultivado en un medio líquido que contenía "Tween 80," se compararon los coeficientes de mortalidad de siete cepas de ratones. A base de uniformidad en los resultados, así como de accesibilidad en grandes cantidades, el ratón de elección resultó ser un ratón albino, con un fondo pardo, no-agutí, el CF 1. La inoculación endovenosa se mostró preferible a la vía intraperitoneal, aun al usar yema de huevo como medio suspensor para el inóculo. Lo mismo que con la selección de la cepa Ravenel del *M. tuberculosis* var *bovis*, la elección del ratón fué considerada como tentativa, pues sólo cabe hacer la selección definitiva cuando se cuenta con el resultado de las pruebas verificadas en este animal con drogas de conocida actividad antituberculosa en el hombre (7).

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# THE USE OF THE MOUSE IN A STANDARDIZED TEST FOR ANTITUBERCULOUS ACTIVITY OF COMPOUNDS OF NATURAL OR SYNTHETIC ORIGIN<sup>1</sup>

## III The Standardized Test

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### INTRODUCTION

In previous papers (1, 2) information has been presented on data leading to the selection of the Ravenel strain of *M. tuberculosis* var. *bovis* and the CF1 homozygous strain of albino mice for use in a standardized test for antituberculous activity of compounds. These reports contained, in addition, evidence as to the best means of maintaining the culture as well as to the optimal dose of culture and route of administration.

The above information has been utilized in the establishment of a standardized *in vivo* test by which compounds of both natural and synthetic origin are tested both orally and parenterally for activity against infection due to *M. tuberculosis*. Such *in vivo* tests for activity are carried out on compounds first selected on the basis of tests *in vitro* and at doses indicated by preliminary tests for toxicity, or rather, acceptability, by the mouse.

The standard techniques, together with some characteristic results will be described below.

### MATERIALS AND METHODS

The strain used is the Ravenel strain of *M. tuberculosis* var. *bovis*. The reasons for the choice of this strain, together with the standard methods of transferring and maintaining the culture so as to assure constant and maximal virulence and of preparing the infecting inoculum, are given elsewhere (1). Similarly the reasons for the choice of the CF1 mouse, together with data bearing on the selection of age and weight ranges and sex are discussed elsewhere (2). For the final standard test a weight range of 16 to 18 grams was adopted.

#### *In vitro* Test

Drugs to be tested *in vivo* are selected on the basis of *in vitro* activity against *M. tuberculosis* var. *bovis* strain BCG, except where other considerations would lead to the belief that a drug might be effective *in vivo*.

The culture is maintained and passed weekly in the following medium:

Na <sub>2</sub> HPO <sub>4</sub>	3.0 Gm
KH <sub>2</sub> PO <sub>4</sub>	4.0 Gm
MgSO <sub>4</sub>	0.6 Gm
Sodium citrate	2.5 Gm
Asparagine	5.0 Gm

<sup>1</sup> From the Division of Microbiology, The Squibb Institute for Medical Research, New Brunswick, New Jersey.



Iron ammonium citrate	0.05 Gm
0.05 per cent solution of Tween 80	0.5 ml
Glycerine	20 ml
Distilled water	1,000 ml

The medium is sterilized at 15 pounds for fifteen minutes in lots of 100 ml per flask. To each flask is added 0.4 ml of 25 per cent bovine serum albumin fraction V sterilized by filtration. The flasks contain a 1½ inch finishing nail sealed in a glass tube as a stirrer. Ten ml of a refrigerated culture not over 30 days old are used as inoculum. The flasks are incubated for 96 hours at 37°C and stirred three times daily for a period of approximately one minute on a magnetic stirrer.

A control for purity of culture is performed by subculturing 0.5 ml from each flask into a tube of beef heart infusion broth.

For the test, the above medium, but without the iron ammonium citrate and with only 0.05 per cent serum albumin fraction V, is used. Two ml of the 96 hour culture described above are added per 100 ml of test medium.

Substances to be tested are used at twofold dilutions. Two ml volumes are used and the maximal concentration of drug is 0.6 mg per ml if the substance is freely soluble. Tests are incubated for 112 hours at 37°C in a well humidified incubator. A standard compound 1-hydroxy 2(1H)-pyridone of known activity (3, 4) is included in every test. Results are read on the basis of turbidity (growth) in the tubes at the end of incubation. If a sharp end point is obtained with no turbidity in one tube and heavy growth comparable to that in the controls in the next tube in sequence, the inhibiting concentration is recorded as interpolated between these two tubes. When a tube of weak growth separates heavy and zero turbidity, it itself is taken as the end point. Results are reported in terms of minimal inhibiting concentrations.

### *Toxicity Test*

Before testing a drug against the infection with tubercle bacilli in the mouse, an approximate idea of its toxicity (acceptability) is obtained. Four mice are used per dose of drug and each drug is tested at two levels, usually at a fourfold difference, until the maximal acceptable level is determined. Acceptability is judged by weight change in the individual mice. All mice are young 16 to 18 Gm animals still actively growing. Failure to gain weight, or actual loss, is an indication of toxicity or unpalatability of the diet, or both. On first assay in the diet, one per cent is the maximum concentration used. The drug is intimately mixed with pulverized Rockland Farm mouse pellets and placed in special stainless steel food cups (4). The food cups are weighed daily and a record kept of the food consumed per 4 mice. When diet toxicities are being investigated the test runs for four days.

Parenteral toxicity is determined by subcutaneous injection. Groups of 4 mice each are used and the two levels tested (in one injection daily) are at a fourfold difference. The injections are continued for seven days and the weight curves of the individual mice followed during that period. The maximal level allowing normal weight gains is thus determined.

### *In vivo Test*

In the infection, test drugs are administered either intimately mixed in the diet or by subcutaneous injection once daily. Two levels are usually tested at a fourfold difference. All treatments are for twenty-one days. For treatment, mice weighing 16 to 18 gm are in groups of 10 in one cage. Twenty untreated but infected control mice in two cages are included in each test. The mice are placed on the diets forty-eight hours prior to infection. When treatment is by subcutaneous injection, the first such injection is made directly after infection. All mice are infected by the injection of 0.5 ml of the standard inoculum (1) into the tail vein.

The average weight of each group of 10 mice is determined daily for 12 days and every

other day thereafter. The special food cups (4) are filled to 350 Gm gross weight every day during the treatment period and the daily food consumption recorded. Autopsies are performed on all mice that die. Information is obtained and recorded on average survival time, per cent survival for 35 days, and  $t_{50}$ . The  $t_{50}$  is the calculated survival time of 50 per cent of the mice. The figure is obtained by plotting on arithmetic-probability (probit) paper (2).

### Care of Personnel

All persons concerned with the infection of mice wear protective goggles. The infected mice are housed in a room liberally equipped with Westinghouse Sterilamps WL-782, style No 1121051-A. Individuals about to work on the program receive a tuberculin test before starting work. If this is negative, they are offered BCG vaccination. All those actively engaged in the program have a complete physical examination together with a roentgenogram of the chest every six months. No cases of laboratory infection have occurred so far.

### RESULTS

*In vitro tests.* Although the results of the *in vitro* test outlined above are used as a guide to selection of drugs for test *in vivo*, the shortcomings of the test and the possible errors involved by such a selection are fully recognized. Since twofold steps are employed, and only enough repetitions run to establish that the end points obtained are of the right order of magnitude, no differences between compounds of less than fourfold are to be considered as significant. Moreover, as will develop when the results with chemical series of compounds are discussed in later papers, although the *in vitro* results may be used directly as to an indication of choice within a given series, they are of woefully little significance in selection between compounds of different series. This is to be expected. The *in vitro* results signify only the activity of the given compound when brought into contact with the tubercle bacillus in the test tube and under the conditions of the test. In the mammalian body many other factors come into play such as absorption and distribution in an unchanged or, at least, still active form, penetration to the site of infection, and maintenance at such a site in sufficient concentration and for sufficient time. Limiting factors such as systemic or local toxicity also play a part.

The validity of using a bovine organism for both the *in vitro* and the *in vivo* studies in a search for a chemotherapeutic drug active in human infection might be questioned. At least in the United States, the overwhelming majority of cases are due to the human variety of *M. tuberculosis*. The *in vitro* sensitivity of *M. tuberculosis* var. *bovis* strain BCG and *M. tuberculosis* var. *humanis* strain H37 Rv have been compared against a series of compounds. The ratio of activity of the drugs against BCG as contrasted with that against H37 Rv was remarkably constant considering the low statistical significance of the actual figures from which these ratios were obtained (see above). In general the ratio of drug required to inhibit BCG as compared to H37 Rv was 0.47, i.e., BCG was from two to three times more sensitive. In 88 per cent, the ratio lay between 0.22 and 0.8. Only 4 per cent of compounds were of equal activity on both organisms or of greater activity against H37 Rv. These figures indicate that results which are not grossly misleading, as far as the ultimate goal of human therapy is con-

cerned, are likely to be obtained by using BCG. Slightly more activity will be suggested by the results than is perhaps entirely justified. No active compounds are likely to be missed. The benefits from use of BCG are a more rapid test, and safety of a considerable number of semi-skilled technicians carrying out the *in vitro* tests.

*Toxicity tests* As has already been indicated, the toxicity tests on the drug given in the diet, but not those on the drug injected subcutaneously, should be regarded as tests of both acceptability (or palatability) and toxicity, or of either, rather than of toxicity alone. Objection might be raised to the small number of mice used in the diet tests for toxicity and the short period of observation time. These objections are recognized but have been overruled in favor of keeping the amount of drug required for first evaluation of worth at as small a quantity as possible, i.e., from 18 to 20 Gm.

In practice it was found that 16 per cent of the time the higher drug concentration fed in the actual test was not fully acceptable (or toxic) on the basis of quantity of food eaten during the first seven days after infection (see below), but in only 1.6 per cent of the cases was it not fully acceptable (or toxic) at both levels when the difference in level was four fold. The acceptability test, therefore, was an adequate guide to the diet levels to be employed in the *in vivo* test, the prime purpose for which it was used.

*In vivo results* As pointed out above, information is obtained on the average survival time of the mice, the  $t_{50}$  (calculated time of death of 50 per cent of the mice), the per cent surviving 35 days, and the averaged curve of weight response. In addition, autopsies are performed on all mice dying. The latter is for purposes of certification as to cause of death only. No attempt has been made to develop a score system of lesions such as is used so extensively in this and other infections to determine the norm and departures from this norm. In our opinion nothing is learned, for the purposes of the present test, by this subjective method of calculation which is not given better by the other, completely objective, methods of calculation. Such a conclusion, however, in no way argues against the obvious value of complete pathological examinations carried out to investigate the activity of any promising drug which emerges from the screen at present under consideration.

The data on the weight response have not been found particularly useful in the quantitative estimation of degree of activity. Certain useful data have, however, emerged. As will be discussed in more detail below, for many reasons tests 1 to 13 inclusive have not been considered in the overall evaluation of the results and only tests from 14 onwards have been used. One indication of the change that occurred between tests 13 and 14 is shown in figure 1. As will be seen in this figure, which shows the averaged weight response of the control untreated mice, the striking feature of the response curve of the early tests is the lack of significant gain in weight in the early part of the curve or of rapid loss in weight later. Surprisingly perhaps, the weight curves of the control mice in the three tests in the series 14 to 52, which were not entirely satisfactory, also show this lack of early weight gain. As can also be seen in figure 1, an active drug, in this

case p-aminosalicylic acid (PAS) at 0.75 per cent in the diet, shows a curve of weight response which by the tenth day has departed sufficiently from the curve of the untreated mice to be significant. Thus it is possible by watching the weight curves to foretell in many instances as early as the tenth day after infection whether an unknown drug is going to show activity or not. Such a sign of activity is only qualitative, however, and in our experience cannot be quantitated.

As indicated, some attention has been paid to survival for 35 days or longer. In 800 control untreated mice, 2 (0.25 per cent) survived, one for 35 days and one for 36 days. Both were in tests in which the control group was otherwise unsatisfactory. On the other hand, some of the active compounds give significant survival at 35 days, *i.e.*, 14 days after drug administration was discontinued. Thus with Promin at 1.0 per cent in the diet, 19 out of 110, or 17.3 per cent, sur-

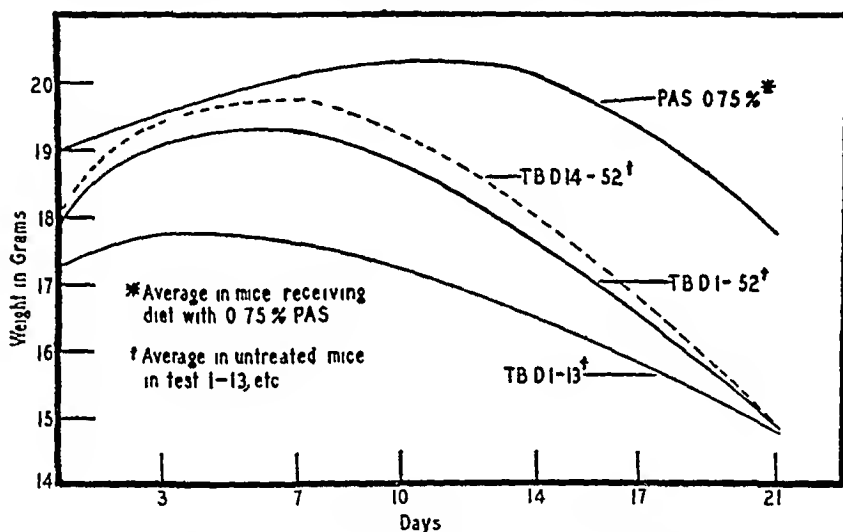


FIG 1 Weight response curves in untreated and treated mice

vived 35 days or longer and one animal survived 56 days. At 0.5 per cent in the diet, 6 of 60, or 10 per cent, survived. With PAS, 7 of 80 (8.8 per cent) survived 35 days at 1.0 per cent diet, 12 of 310 (3.9 per cent) at 0.75 per cent diet, and one of 300 (0.33 per cent) at 0.375 per cent diet. With streptomycin at a single subcutaneous dose of between 6,000 units and 22,500 units per Kg per day, 18 of 80 survived and, with dihydrostreptomycin at the same levels, 22 out of 90 survived. In the case of these antibiotics, survival to 60 days and beyond was not unusual. Two things, therefore, are clear. With active drugs such as the four discussed above significant survival beyond 35 days does occur. The conditions of the test are so severe, however, that only reasonably active compounds and reasonably high doses of such compounds give such survival and this criterion, therefore, is of little use in a preliminary screening program such as the one at present under consideration.

Finally consideration has been given to both the mean survival time and the  $t_{50}$  (calculated survival time of 50 per cent of the mice). The figures for the

control untreated group are shown in table 1. The results are broken down into the probable error of those from 1 to 13 and of those from 14 to 52 (the latter being current at the time of writing). As has already been indicated above, certain changes occurred between tests 13 and 14. One was that a change in the shipping and preinfection care of the mice was adopted and the other that a change was made in the preparation of the infecting inoculum.

In tests through 13, culture continuously transferred at weekly intervals was used. Such weekly transfer resulted in a gradual fall in virulence. As soon as this change was detected, only cultures of previously proved virulence were used. The change in preinfection handling of mice also seemed to have an effect. Thus the per cent rate of nonspecific deaths dropped from 4.1, which it was for the 2,320 mice used in tests 1 to 13, to 1.1 per cent for the 7,460 mice in tests 14 to 52. Whether due to one or the other of the two changes outlined, a marked difference was noted in the untreated groups of infected mice. The change in weight response has been noted above (see figure 1). The change in the  $t_{50}$  and the mean survival time with the satisfactory decrease in the probable error of a single experiment is noted in table 1.

TABLE 1  
*Probable Error of Mean Survival Time and  $t_{50}$  of Control Mice*

	TEST 1 TO 13	TEST 14 TO 52
$T_{50}$	20.45 $\pm$ 2.29 days	19.86 $\pm$ 0.72 days
Mean survival time	21.89 $\pm$ 3.17 days	20.44 $\pm$ 0.73 days

It is clear from table 1 that the results are at least as satisfactory with the  $t_{50}$  as with the mean survival time. Since the  $t_{50}$  can be read sooner than the mean survival time, and also, since the  $t_{50}$  allows of less error being introduced, particularly in the treated groups by reason of the undue survival of one mouse, the  $t_{50}$  has been selected as the most satisfactory objective criterion by which to record and judge the results.

Because of the above, it has seemed justifiable to consider only experiments subsequent to test 13 as representing the established and satisfactory technique and only these have been and will be considered in the evaluation of active compounds.

*Active drugs.* P-aminosalicylic acid is the compound which, on the basis of early comparative evaluation in this test, has been selected as the standard active compound for oral administration. More data are available on it than on any other compound. It was soon found that, despite statements to the contrary, this drug is highly active against infection of mice with bovine strains of *M. tuberculosis*. Table 2 and figure 2 give the information obtained on the activity of PAS. On the whole, the reproducibility of both drug intake and response in  $t_{50}$  is remarkably uniform and PAS is obviously suited to serve as a standard active drug. According to the data obtained, moreover, the activity of the drug, as indicated by the  $t_{50}$ , appears as a straight line when plotted on arithmetic

paper from an intake of 2.77 to one of 12.77 M moles per Kg per day. Below an intake of 2.77 M moles, the activity falls off rapidly

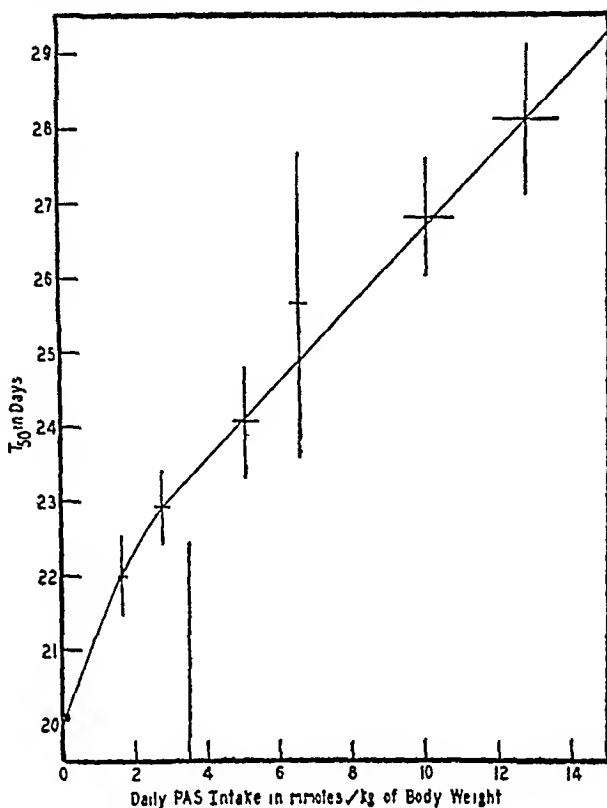


FIG 2 Dose response curve for PAS

TABLE 2

*Drug Intake and Activity of Various Diet Concentrations of PAS, together with Probable Error (PE) and Mean Error of the Mean (ME)*

CONCENTRATION IN DIET	NUMBER OF TESTS	DRUG INTAKE/DAY/M MOLES PER KG	T <sub>50</sub> IN DAYS
<i>per cent</i>			
0.125	4	1.67 ± 0.09 PE ± 0.04 ME	22.0 ± 0.55 d PE ± 0.27 d ME
0.2	4	2.77 ± 0.18 PE ± 0.09 ME	22.92 ± 0.5 d PE ± 0.25 d ME
0.25	4	3.51 ± 0.06 PE ± 0.03 ME	20.08 ± 2.38 d PE ± 1.19 d ME
0.375	30	5.06 ± 0.34 PE ± 0.06 ME	24.06 ± 0.74 d PE ± 0.13 d ME
0.5	4	6.54 ± 0.23 PE ± 0.11 ME	25.65 ± 2.05 d PE ± 1.02 d ME
0.75	31	10.08 ± 0.66 PE ± 0.12 ME	26.81 ± 0.79 d PE ± 0.14 d ME
1.0	8	12.77 ± 0.89 PE ± 0.32 ME	28.11 ± 1.0 d PE ± 0.35 d ME

Promin was also included on several occasions in tests 14 through 52. Thus a diet concentration of 0.063 per cent was tested four times, 0.125 per cent once, 0.5 per cent six times, and 1.0 per cent eleven times. The results are shown in ta-

ble 3 The number of replicates run is probably not sufficient to construct any significant response curve All that can be said is that there is no evidence from the data at present at hand that the response curves for Promin and for PAS have a similar slope, a point of considerable importance in considering the results obtained with these and other compounds

Two drugs, streptomycin and dihydrostreptomycin, were run as standard drugs for daily subcutaneous therapy The results obtained are shown in table 4 It will be noted that the responses with the two antibiotics are almost identical Here again the number of replicates are small and may be insufficient for

TABLE 3

*T<sub>50</sub> Response of Promin at Different Levels of Drug Intake by Mouth*

CONCENTRATION IN DIET	NUMBER OF TESTS	MEAN DRUG INTAKE PER DAY	MEAN T <sub>50</sub>
<i>per cent</i>			
0.063	4	0.16 M moles/Kg	21.23
0.125	1	0.32 M moles/Kg	21.8
0.5	6	1.37 M moles/Kg	25.65
1.0	11	2.70 M moles/Kg	27.65

TABLE 4

*T<sub>50</sub> Response of Streptomycin and Dihydrostreptomycin at Different Levels of Drug Intake per Subcutaneous Injection*

DRUG INTAKE M MOLES/KG	STREPTOMYCIN		DIHYDROSTREPTOMYCIN	
	Number of tests	Mean T <sub>50</sub>	Number of tests	Mean T <sub>50</sub>
0.0076	—	—	1	25.2
0.0091	2	26.8	2	26.2
0.0173	2	27.5	2	27.9
0.026	2	30.2	2	29.5
0.039	2	32.5	2	33.4

the construction of response curves However, there is no evidence that the slope of the response curves for these two antibiotics would resemble that for PAS

It has thus been possible to measure in the standardized test with the Ravenel strain and the CF1 mouse the response of drugs such as streptomycin, dihydrostreptomycin, or p-aminosalicylic acid of known antituberculous activity in man The response which has been obtained with these compounds in the murine infection is such as to encourage one to believe that results roughly parallel to those to be expected in man can be obtained by the use of this test At least the parallelism of the response to that seen in man would appear to be as satisfactory as any that can be claimed for those tests using the guinea pig or the rabbit

## DISCUSSION

The results obtained with this tuberculous infection in mice are remarkably uniform and reproducible whether one considers the behavior of the untreated controls or the response to treatment with active drugs. It is appreciated that this *in vivo* test is highly dissimilar to the natural infection in man or in any other animal, but it is submitted that this is of comparatively little importance, particularly at a level of investigation where search is being made for active drugs or series of drugs. When such active drugs emerge, a different type of test can be used merely by changing the conditions of the strain of mouse, strain of organism, infecting dose, and so forth. As was pointed out elsewhere, the infection in the mouse can be made to conform to almost any pattern desired, from a rapidly fatal septicemia without many lesions to a chronic fibrocaceous disease.

Actually, the test is no more dissimilar to its natural counterpart than countless dozens of other chemotherapeutic tests (with organisms producing either acute or chronic infections) which are employed daily and on the results of which definite decisions as to human or veterinary usefulness are reached. Such decisions are usually confirmed on clinical trial. There is certainly no reason, other than custom and reiteration, to believe that the tuberculous infection which employs the guinea pig is more satisfactory in indicating human (or veterinary) usefulness. Moreover, no one can doubt that this latter animal is less satisfactory for many reasons, such as higher initial and continuing expense, lack of homozygosity of available strains, and larger amounts of drug required.

With the test as outlined above, a purely objective criterion, the  $t_{50}$ , is used in evaluating the results, and any possibility of errors due to the personal factor is eliminated. Subjective criteria involving scoring based on a personal evaluation of the observed lesions would seem to be open to many objections and surely should not be considered if a satisfactory objective criterion is available. It is believed that the above presentation shows that satisfactory objective criteria are available and that of these the  $t_{50}$  is the best.

As has already been pointed out, both gross and microscopic pathological data find their true usefulness in the evaluation of any active compound which emerges, and will be thoroughly explored under such circumstances.

## SUMMARY

Information is presented on the results obtained by the use of certain standardized procedures for the evaluation of antituberculous compounds *in vitro* and *in vivo*.

The use of a homozygous mouse (the CF1) and a bovine strain of *M. tuberculosis* (Ravenel) has allowed the development of a test which shows good reproducibility both in the untreated infected mice and in the mice treated with known active drugs. Small numbers of mice are used and the results can be evaluated in under four weeks. Compounds of unknown antituberculous potential are now being tested by the above methods and the results will be presented later.



## SUMARIO

*Empleo del Raton en una Prueba Normalizada de la Actividad Antituberculosa de los Compuestos de Origen Natural Sintético III La Prueba Normalizada*

La informacion presentada abarca los resultados obtenidos con el empleo de ciertos procedimientos normalizados para la valuación de los compuestos anti-tuberculosos *in vitro* e *in vivo*

El empleo de un ratón homólogo (el CF1) y de una cepa bovina del *M. tuberculosis* (Ravenel) ha permitido elaborar una prueba dotada de buena reproducibilidad en los ratones, tanto infectados y sin tratar como tratados con drogas activas conocidas. El número de ratones usados es pequeño y el resultado puede ser apreciado en menos de cuatro semanas. Con las técnicas descritas se hallan ahora en comprobación compuestos de desconocida actividad anti-tuberculosa, y el resultado se presentará después.

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# THE USE OF BIOMETRIC METHODS IN COMPARISON OF ACID-FAST ALLERGENS

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In allergen studies, comparisons of potency are of great importance. They have been a matter of concern to U S Department of Agriculture workers on tuberculosis and related infections in cattle.

Johnson and associates (3) have published studies on multiple testing of allergens on sensitized cattle, measuring reactions by skin thickening. During 1945 and 1946 some trials of technique were made and the results were analyzed. The work was done in cooperation with Dr H W Johnson, Dr A H Groth, and Dr A B Larsen of the U S Bureau of Animal Industry's Regional Animal Disease Research Laboratory, Auburn, Alabama, and Dr L A Baisden and Mr R R Henley of the Washington office of the Pathological Division of the Bureau. The same methods of analysis have been found applicable to skin reactions on guinea pigs, measuring reaction by diameter or area of skin affected. The writer (6), has written a discussion of applications of experimental design to these problems.

## BASIS OF COMPARISONS

The use of biometric methods is not so complex as is often believed. The basic reason for thinking one material is better than another is that it consistently gives better results in repeated trials. Statistical analysis simply gives mathematical expression to the consistency or lack of consistency. A measure of variability familiar to many investigators is the standard deviation. In present day work the *variance*, the square of the standard deviation, is much used, since it is more convenient arithmetically and since variances from different sources are additive. By the use of the technique known as *analysis of variance* (described by Snedecor (5)), variances from different sources may be separated and compared when the experimental plan permits it. Care in planning an experiment is necessary to permit a separation of all pertinent effects.

In comparing the potencies of preparations by their biological reactions, the basis of comparison is the ratio of concentrations required for a given effect. A material affording a particular result with only one-tenth as high a concentration as another material must be ten times as potent as the other material. In present day work, the reactions are usually compared by analysis of variance and related to the concentrations by a curve. Interpolation on the curve gives the best estimate of concentration required for a given reaction. A carefully planned experiment will permit several short cuts. These methods are discussed in numerous articles by Bliss and associates. A particularly specific and useful treatment is by Bliss and Marks (1). This sort of comparison is termed biological assay.

In analysis of the trials of technique of testing tuberculins on cattle, it was found that there was little variation in the operators' inoculations and measure-

ments, or between the two sides of an animal. There were marked differences in reaction between cows, and also differences between regions of the body. A good experimental plan will balance out these differences by giving materials equal representation on all the areas and the animals used.

Varying concentrations of a material showed marked differences. A long series of dilutions, amply replicated, was tried out and the results were studied. Dilutions ranged from 1:20 to 1:1,536,000 O.T.<sup>1</sup> The relation of concentration and reaction was not linear. However, the logarithms of concentration plotted against reactions gave a nearly linear curve, though it appeared faintly S-shaped.

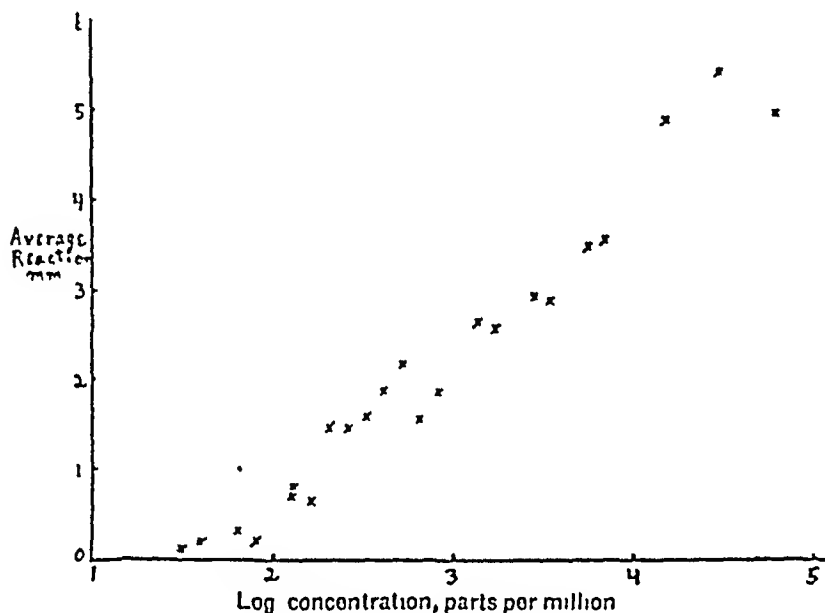


FIG. 1. Relation between log concentration and reaction.

Typical results, large series of concentrations, 4 cows, 12 sites per concentration, tuberculin precipitate on para sensitization. (Site differences cause a wider scatter than should be found, but trend still shows up.)

(figure 1) At lower concentrations the slope was less steep. Linearity was good, however, over a wide range of medium and high strengths. The linearity of reaction with log concentration was used in analysis. Heterologous materials gave curves less steep than homologous materials. For example, tuberculin on tuberculin-sensitized cattle gave a steeper curve than johnin on such animals. The two types of curves were well separated at high concentrations and seemed to converge at lower ones. A rather high level of reactions seems desirable in comparing allergens.

#### EXAMPLE OF TYPICAL DATA

As an example, a test of a johnin (30-I-3) against its silicotungstic acid precipitate on five paratuberculosis-sensitized cows is selected. One side of each

<sup>1</sup> O.T. = Old Tuberculin, as originally prepared by Koch.

cow was injected with the parent material, the other with the precipitate, each in a number of corresponding sites. The sites on each side were divided into 14 groups of 3 adjacent sites each. Each group of three received three concentrations (1 40, 1 400, 1 4,000 O T), one on each site. Reactions to the six treatments (two materials at three concentrations) are averaged for each cow. Although the 14 units of a treatment on each cow were on different areas, varying in reaction, the units of each treatment covered the same areas. Hence, the averages are comparable.

## ANALYSIS OF VARIANCE

The analysis of variance must first separate variance for cows, for treatments, and for residual error. In this experimental plan, the error variance is that for

TABLE 1

*Average Reactions in Millimeters of Increased Skin Thickness in Test of Johnin vs its Precipitate*

COW NUMBER	PARENT MATERIAL			PRECIPITATE			TOTALS
	1 40	1 400	1 4,000	1 40	1 400	1 4,000	
816	10 1	4 5	1 5	12 0	7 4	3 1	38 6
817	8 0	5 0	2 2	9 9	6 5	3 5	35 1
818	10 5	5 4	2 5	15 2	7 9	3 7	45 2
819	12 6	5 4	2 6	13 4	7 9	4 3	46 2
820	6 6	2 5	1 2	7 7	4 3	1 6	23 9
Totals	47 8	22 8	10 0	58 2	34 0	16 2	189 0
Mean	9 56	4 56	2 00	11 64	6 80	3 24	

The totals are given merely for convenience in analysis, they would not normally be entered in the table.

*interaction*, or differential effect of cow and treatment. If treatments behave differently on some cows than others, the error will be high and will indicate that there is doubt that treatments are really different. The error variance is really a measure of how much treatments might vary, if they were not in fact different at all.

Calculation is carried out by convenient short cut methods. The variance is the square of the standard deviation, and methods for calculation are similar. First must be calculated the total *sum of squares of deviations* of all items from the general mean. This sum is then subdivided according to sources of variation. The portions are divided by the proper divisors ("degrees of freedom," one less than the total number). The quotients are the "mean squares" or *variances* expressing variation due to each source. The variances may be compared by a standard test (Snedecor, cited above).

To get the total sum of squares of deviations, all items are squared and the squares totaled. From this total is subtracted a "correction factor," which is the sum of the items squared and divided by their number. This subtraction

reduces the sum of squares of original items to the sum of squares of *deviations* from the mean. In our material the calculation is

$$[(10.1)^2 + (1.5)^2 + \text{et cetera} + (1.3)^2 + (1.6)^2] - (189.0)^2/30$$

or 1618.76 minus 1190.70, which is 428.06

The portion of this sum of squares due to cow variation is quickly computed from cow totals by another short cut formula  $[(35.6)^2 + \dots + (23.9)^2]/6 - 1190.70$ , or 51.11. (The divisor is 6, because 6 items enter each total.) The portion due to treatment variation is estimated

$$[(17.8)^2 + \dots + (16.2)^2]/5 - 1190.70 \text{ or } 351.37$$

The portion due to differential effect or experimental error is conveniently estimated by subtracting the others from the total. (It could be estimated directly by more complex methods.) It is  $428.06 - 51.11 - 351.37$ , or 22.28. A summary of the analysis to this point may be seen in table 2.

TABLE 2  
*Summary of Analysis of Variance*

SOURCE OF VARIATION	NUMBER OF ITEMS OR GROUPS	DEGREES OF FREEDOM	SUM OF SQUARES	MEAN SQUARE
Total	30	29	428.06	—
Cows	5	4	51.11	13.60
Treatments	6	5	351.37	70.27
Error	—	20	22.28	1.11

The ratio of "cow" or "treatment" mean square to "error" mean square may be compared with the tabular "F" value (Snedecor (5, ch. 10)). Both are very significant.

#### REFINEMENTS IN ANALYSIS

Further study is necessary to define the important effect of treatments. It is easy to see that nearly all the effect is due to difference between concentrations, and that it is doubtful how much is due to materials. The sum of squares between treatments could be subdivided, using an extension of methods already shown. The special arrangement of the material, however, makes possible a study by easier methods which are well adapted to such problems. This is the method of separation of sums of squares for individual degrees of freedom discussed by Snedecor (5, ch. 15). Bliss and Marks (cited above) give the special application to the present problem.

It is noted above that reactions show a nearly linear relation with logarithms of concentration. The three concentrations (1.40, 1.400, 1.4,000) are more clearly stated as parts per 10,000 (250, 25, and 2.5). The logarithms of these are 2.4, 1.4, and 0.4 respectively. This equal spacing of logarithms makes possible a special application of single degrees, to separate the part of the sum of squares due to linear relation, or regression, with logarithms of concentrations. Other parts of interest may also be separated.

In the single degree method there are several general rules as to arrangement of comparisons, divisors, et cetera. The arrangement suited to this problem is presented in table 3.

TABLE 3  
*Single Degree Analysis of Treatments (Data of table 1)*

	MATERIAL AND LOG CONCENTRATION (PARTS PFR 10,000)						NET SUM	DIVISOR	SUM OF SQUARES = (NET SUM) <sup>2</sup>
	Parent			Precipitate					
	2 4	1 4	0 4	2 4	1 4	0 4			
	Reactions sum								
	47 8	22 8	10 0	58 2	34 0	16 2			Divisor
Material	+1	+1	+1	-1	-1	-1	-27 8	30	25 76
Regression (linear)	+1	0	-1	+1	0	-1	+79 8	20	318 40
Non-parallelism	+1	0	-1	-1	0	+1	- 4 2	20	0 88
Curvature	+1	-2	+1	+1	-2	+1	+18 6	60	5 77
Opposed curvature	+1	-2	+1	-1	+2	-1	+ 5 8	60	0 56

It will be noted that these sums of squares add to the previous total for "treatments" in table 2 (351.37).

The sums of squares for each degree of freedom is obtained by taking the net sum indicated by the signs, squaring it, and dividing by the correct divisor. The divisor is the sum of squares of the coefficients, multiplied by the number of replications. For example, for "curvature," the net sum is [(+1) (47.8)] + [(-2) (22.8)] + [(+1) (10.0)] + [(+1) (58.2)] + [(-2) (34.0)] + [(+1) (16.2)], which equals +18.6. The divisor is 5 [(+1)<sup>2</sup> + (-2)<sup>2</sup> + (+1)<sup>2</sup> + (+1)<sup>2</sup> + (-2)<sup>2</sup> + (+1)<sup>2</sup>], or 60. The sum of squares is (+18.6)<sup>2</sup>/60, or 5.77.

These sums of squares are also mean squares because each is based on only one degree of freedom. As mean squares, they may be compared to the general error variance, 1.11, in the F test. This test shows the difference between materials to be quite significant, the variance due to linear regression is outstandingly important, variance due to curvature is barely significant and of small importance. The linear relation accounts for most of the trend. The other two variances are nonsignificant, parallelism of trends in the two materials is satisfactory, and no trace of "opposed curvature" appears.

It has been noted that this simple analysis could not be carried out if concentrations were not equally spaced on the log scale used. With unequal spacing, certain single degrees of freedom could be defined, but they could not be directly identified with linear regression, curvature, et cetera. Also, the part of the variation due to linear trend could be evaluated, but it would have to be done by general methods, fitting a line and taking deviations from it (Snedecor (5, ch. 6)).

#### MEASURING POTENCY

The analysis shows that materials are really different, by comparison of their variance with the error variance. To measure the *extent* of the difference, further analysis is needed. The comparison of concentrations needed for a given effect

is the vital one. These concentrations can be estimated from curves showing relation of concentration and reactions. The linear relation with logarithms of concentration makes it simple to estimate the *difference* in logarithms, and later express this as a *ratio* of concentrations. The line expressing this relation is called a regression line. The fact that regressions are practically parallel for the two materials makes the distance between the lines a measure of the difference desired. (If they were not parallel a statement of difference could be made only for a given level of response.)

Regressions could be fitted directly, and estimates of log difference made by general methods. However, there have been developed short cut methods, if experimental arrangement makes possible the analysis of table 3 and if nonparallelism and curvature are not important. Bliss and Marks (cited above) illustrate these convenient methods. The difference in logarithms is estimated as  $\bar{C}_2 - \bar{C}_1 + (KID)/B$ , where  $\bar{C}_2$  and  $\bar{C}_1$  are average concentrations of the test and standard substances,  $I$  is the interval between logarithms of concentration,  $K$  is a constant depending on number of concentrations used,  $D$  is the square root of variance between materials, and  $B$  the square root of the variance for linear regression. Here  $\bar{C}_2$  and  $\bar{C}_1$  are equal and  $I$  is simply 1, so that the expression boils down to  $KD/B$ . For three concentrations,  $K$  is  $\sqrt{8/3}$  or 1.63, for two concentrations, 1, for four concentrations,  $\sqrt{5}$ . Thus our estimate of log difference is  $(1.63 \sqrt{25.76})/\sqrt{318.40}$ . This is  $8.28/17.84$ , or 0.464. It may be stated as +0.464 in evaluating the potency of the precipitate compared to its parent material. A reversal of the test would change the sign. The antilogarithm of 0.464 is 2.91. We estimate that 2.91 times as much parent material as precipitate is required for the same effect. Hence, the precipitate has a potency estimated as 2.91 times that of the parent material.

#### ERROR OF POTENCY DETERMINATION

Finally, it is desirable to estimate the standard error of the potency ratio. This may be readily done in terms of logarithms. A short cut formula (Bliss and Marks) is available for solutions of the type used above. The standard error is  $(s/b) \sqrt{2/N}$ , where  $s$  is the standard deviation, square root of the error variance (here 1.11),  $b$  is the average regression coefficient of reaction on log concentration,  $N$  is the total number of trials of each material (here 15). A more complex formula is used where  $\bar{C}_1$  and  $\bar{C}_2$  are unequal. To use the error formula, we must estimate the average regression coefficient. It can be calculated in this simple analysis as the quotient of "net sum" over "divisor," but a more general method is given. The coefficient for each material can be quickly calculated from logs of concentration and average associated reactions. It is the sum of products of deviations of these two variables, divided by the sum of squares of deviations of logs of concentration. The sum of square of deviations of logs is quickly calculated  $(0.4)^2 + (1.4)^2 + (2.4)^2 = (0.4 + 1.4 + 2.4)^2/3$ , or 2.00. In this particular case this might be easily calculated by taking deviations directly from the mean, 1.4, squaring and summing. The sum of products mentioned, for the parent material, is  $(9.56 \times 2.4) + (4.56 \times 1.4) + (2.00 \times 0.4) = (16.12 \times 4.2)/3$ , or

+7.56 (16.12 is the sum of the mean reactions, 4.2, the sum of logs) The regression coefficient is then  $+7.56/2.00$ , or  $+3.78$ . This is an estimate of slope of the line, for every advance of 1.0 in log concentration, an advance of 3.78 mm. in reaction is expected. The regression coefficient for the precipitate is estimated as  $+4.20$ . The average regression coefficient is  $+3.99$ , which can be used as "b" in the formula, s will be  $\sqrt{1.11}$ , or about 1.054,  $\sqrt{2/N}$  will be  $\sqrt{2/15}$  or 0.365. Thus  $(s/b) \sqrt{2/N}$  will equal 0.096.

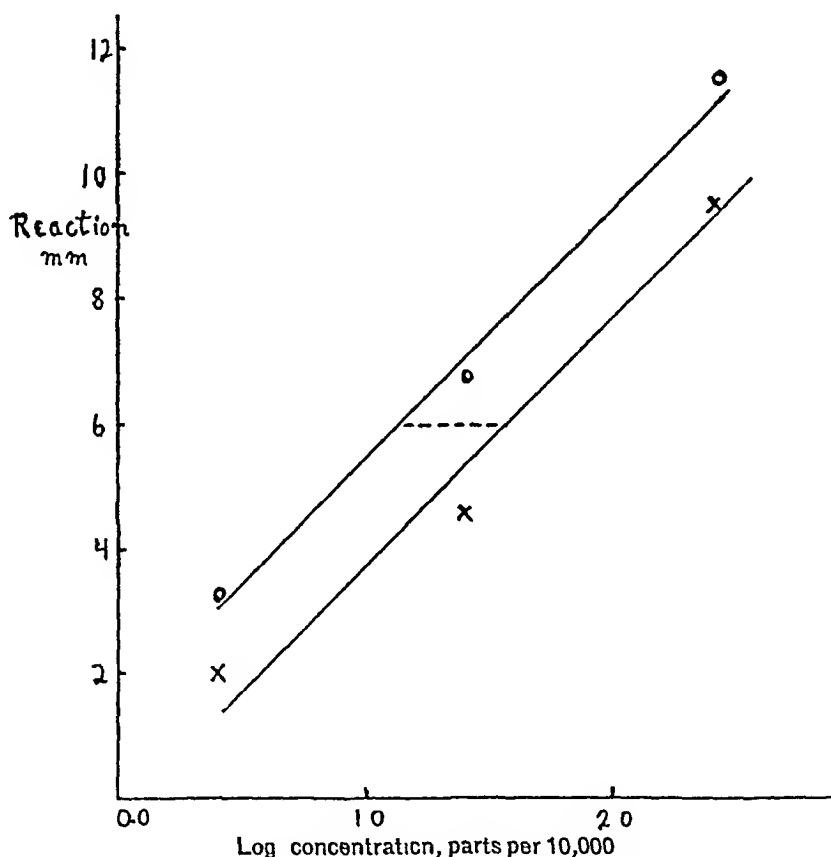


FIG. 2. Average regression fitted to reactions of parent material (X) and precipitate (O) from table 1.

Dotted line shows log potency ratio, graphic determination, as near 0.45.

The log of the ratio is thus estimated as 0.464 with a standard error of 0.096. In figure 2, the mean reactions are plotted against logs of concentration, with the average regression fitted and the distance between the lines measuring the log of potency ratio.

#### EXAMPLE OF WORK WITH GUINEA PIGS

Guinea pigs are frequently used in preliminary evaluations of tuberculins, they often afford a quick and convenient trial (See McIntosh and Konst (4), a letter



from Greene (2) in England also discusses the work further) When the same materials have been tested on both cattle and guinea pigs, rankings have been similar. Results have appeared to be a little less consistent with guinea pigs than with cattle.

Reaction has been measured by size of skin area showing irritation, areas, or average diameters, of the round or oval spots have been used. It seems that linear measurements are more likely to be "normal" and suited for analysis than areas. In the one comparison of the two criteria made in this work, diameters were a little more precise than areas, this question needs more study.

Table 4 shows results of a comparison of 3 B A I tuberculins on each of 4 mammalian-sensitized guinea pigs. Three concentrations were used, thus employing 9 sites per animal, complete randomization was used.

TABLE 4  
*Comparison of Tuberculins on Guinea Pigs*  
(Average diameter of irritated spots in millimeters, 24 hour reading)

FIG NUMBER	TUBERCULIN NUMBER AND CONCENTRATION								
	876			880			881		
	1 100	1 500	1 2,500	1 100	1 500	1 2,500	1 100	1 500	1 2 500
39,152	16 00	13 00	9 00	16 25	10 00	11 25	17 50	11 00	8 25
38,068	15 50	12 00	10 25	16 25	10 50	9 50	15 75	14 25	9 00
38,062	25 00	12 00	11 00	14 25	15 50	11 25	19 50	13 50	8 25
38,075	14 75	13 00	12 00	17 50	10 50	10 00	17 50	15 25	9 25

Following the same methods of analysis as in tables 2 and 3, and comparing tuberculins 880 and 881 with 876 as a standard, logs of potency ratios were 0.20 and 0.07, respectively. Standard errors of logs of potency ratios were 0.18 and 0.16, thus, no real difference was found in the materials.

#### SUMMARY

The application of biometric methods to the problem of comparison of allergens is discussed and an example is presented using results from cattle in detail. A second example of work with guinea pigs is more briefly cited. The results show that biometric methods are not difficult, that they measure consistency and give common sense results, and that experiments must be carefully planned to make full use of biometric aids in interpretation.

#### SUMARIO

#### *El Empleo de las Técnicas Biométricas en la Comparación de los Alergenos Acidorresistentes*

Discutida la aplicación de las técnicas biométricas al problema del estudio comparativo de los alérgenos, preséntanse ejemplos de los principios comprendidos, usando los resultados obtenidos en bovinos y cobayos. El resultado demuestra que las técnicas biométricas miden la constancia y que hay que pla-

near cuidadosamente los experimentos para aprovechar debidamente los auxiliares biometricos en la interpretaci3n

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## EDITORIAL

### Tuberculosis in Medical Teaching

Convincing arguments can be advanced to support the thesis that tuberculosis is the most important among the diseases which are both preventable and curable. To readers of this journal, the reasons do not require iteration why this disease remains one of the paramount medical problems of this century, despite the considerable decline in its mortality in some countries. The importance of the problem is indeed conceded by most leaders in medicine and medical education, and the necessity to instruct students and young physicians in this field is widely recognized. Yet there is, in this country at least, and particularly among physicians who have devoted themselves to the study and treatment of the disease, a growing concern about the adequacy of professional training as it relates to tuberculosis. This concern has manifested itself within the American Trudeau Society by the formation of a Committee on Medical Education. The investigations made and the conferences held by this committee have undoubtedly aided in clarifying the problems, in discovering present deficiencies, and in pointing the way to remedial solutions.

It requires no special investigations, however, to recognize the principal cause of present day inadequacies in undergraduate and postgraduate medical training in tuberculosis. The cause is at once apparent in the relative isolation of this field of medical activity from the teaching centers. The sanatorium movement, which at the opening of the twentieth century was numerically still in its small beginnings, has in the last fifty years succeeded in segregating in special institutions nearly all of the patients under active hospital treatment for pulmonary tuberculosis. Desirable as this may be in other respects, it has created special problems in medical education.

The tuberculosis patients who might serve for clinical instruction have, for the most part, been withdrawn from the teaching hospitals. Consequently, neither the students nor their principal teachers have sufficient opportunity for direct observation and study of this prevalent disease. In many teaching hospitals, pulmonary tuberculosis patients are not admitted or they are rigidly segregated in a special division which serves more as an isolation and transfer depot than as a unit for definitive medical care. Usually such units, like the special tuberculosis hospitals and sanatoriums, are staffed separately from the general medical services. The physicians who undertake the care of these patients are often too overburdened to take as active a part in the general medical work as their colleagues in other branches of internal medicine. Thus a subspecialty of internal medicine has arisen which, though by no means narrow, since it has grown to include pulmonary diseases in general, is further separated in practice from general medicine than are most of the other recognized subspecialties. The other internists, for their part, have small opportunity, and often little interest, to share in the responsibility of caring for the tuberculous

sick. The lack of interest is particularly conspicuous in academic circles and in teaching hospitals, in many of which indeed the attitude appears to be that tuberculosis is scarcely a concern of the internist. In most of the American medical colleges this condition has existed not only through many generations of medical students, but through several professorial dynasties.

In theory, the special status, which the care of tuberculous patients has come to occupy because of the real or assumed necessity for segregation, need not be detrimental to medical education. Courses for undergraduates can be arranged in sanatoriums and tuberculosis hospitals. Affiliations can be provided for the exchange of interns and residents between such hospitals and general hospitals, or between general services and tuberculosis services in general hospitals. Some such arrangements are in fact widely prevalent and it is not the lack of them which constitutes the problem. There is, to be sure, great variation in the quality of instruction and in the amount of time devoted to these courses and training periods in different centers. The particular success achieved in the competition for curriculum time depends in large part on local factors. Neither is the main problem the training of tuberculosis specialists or even of teachers. This must also depend on the organization of tuberculosis facilities in particular communities.

The larger problem is whether the segregation of tuberculous patients, to the extent to which it exists, is necessary and whether the relative isolation of this field of medical activity is greater than it need be in the interest of good care and of scientific progress. Considerations of climate, which initially influenced the selection of remote localities for the establishment of tuberculosis institutions, have been largely discarded. In recent years the infectious nature of the disease and its chronicity have been the main factors in the continued segregation of patients. The latter considerations are still valid and the provision of special facilities is necessary, though these need not be remote. The progress of the last several decades in thoracic surgery and, to some extent also, the more recent developments in chemotherapy, have made the provision of complete hospital facilities essential, either within the tuberculosis institutions themselves or easily accessible. The skills required in the modern treatment of pulmonary tuberculosis are many and varied. The frequent association of tuberculous and nontuberculous complications adds further to the need for practically all medical and surgical specialty services, not excluding research facilities. The closest possible association and interchange of information and ideas between the tuberculosis and general hospitals is for these reasons evidently desirable. Particularly is it desirable for the teaching hospitals, which are the principal centers of clinical research, to maintain active contact with tuberculosis institutions, and even to provide a quota of beds for the interchange of patients.

The admission of tuberculosis patients to general teaching hospitals on a more liberal basis than has become the custom would do more than any other measure to improve medical education in tuberculosis. In a teaching hospital the mere presence of a tuberculosis section, even if limited to 25 or 50 beds, is of educational value. It permits a greater integration of instruction in this subject with instruc-

tion in general medicine and surgery. More importantly, it promotes a better understanding of the disease on the part of the general medical and surgical attending and teaching staff, and a greater awareness of its clinical and research problems. No less importantly, it permits the physicians with a special interest in tuberculosis and pulmonary diseases to pursue the sub-specialty without losing close contact with general medicine. By actual participation in the work of the general services they may not only extend the breadth of their own medical knowledge, but also influence greatly the attitudes of their teaching colleagues.

In the last analysis, it is not what students learn in special courses, but what they absorb from their principal teachers, which forms education. As long as the complacent attitude prevails in the general services that a case of tuberculosis is primarily a disposition problem, so long will the education of students and interns be deficient. Only exceptional circumstances, such as contraction of the disease itself, will readily turn the young physician's interest to a closer study after the conditioning he usually receives in his clinical clerkship and internship.

To the phthisiologists and teachers of tuberculosis, the remedies should be clear. No amount of propaganda about the pre-eminent importance of tuberculosis as a world medical problem is of the slightest value. Neither is insistence on a particular amount of curriculum time desirable or necessary, beyond a reasonable minimum which is not likely to be denied. Rather it is essential to attempt in every way possible to reduce the barriers, both psychological and practical, which have grown up between this sub-specialty and general medicine. By the very nature of the problem, these barriers cannot all be removed nor should special experience and skill in the clinical problems of tuberculosis be surrendered. Greater participation by pulmonary specialists in general medical service and teaching can, however, be developed without sacrifice of special competence. They need not acquiesce in over-specialization if they make it a condition of their service to maintain opportunities for pursuing broader interests. By so doing they can surely improve their own teaching and, not improbably, they may awaken in their colleagues an interest in reciprocal participation.

As tuberculosis, in some aspect, is the concern of every practitioner in whatever specialty, so its teaching is the responsibility of the entire medical faculty. The phthisiologist's concern is with the segment of the problem which lies within the field of internal medicine. As the thoracic surgeon is primarily a surgeon, so the phthisiologist is primarily an internist. The more he can participate with other internists in joint clinical research and teaching enterprises the better will be the education of the students who are under their mutual guidance.

CARL MUSCHENHEIM

## LETTER TO THE EDITORS

### TUBERCULOSTATIC ACTIVITY OF AUREOMYCIN IN VITRO AND IN VIVO

*To the Editors of the American Review of Tuberculosis*

The letter of Steenken and Wolinsky<sup>1</sup> on the activity of aureomycin against the tubercle bacillus prompts a brief note as to the results in our hands. The growth inhibiting action on H37Rv, Ravenel, and a BCG strain of *M. tuberculosis* has been tested *in vitro* Using Kirchner's medium, to which has been added 0.03 per cent of Triton A-20<sup>2</sup>, and reading the test at the end of 5 days, a sharp end point of inhibition has been obtained at 4.55  $\gamma$  per ml for H37Rv, 12.5  $\gamma$  per ml for Ravenel and 0.36  $\gamma$  per ml for BCG in the absence of serum. With 5 per cent sheep serum in the same medium at the end of 5 days, a range of partial inhibition of BCG occurred from 0.27  $\gamma$  to 1.0  $\gamma$  per ml.

The maximal tolerated daily dose of aureomycin *per os* for the CF1 albino mouse weighing approximately 18 Gm was determined and found to be 5 mg. Groups of 10 mice each of the same CF1 strain weighing approximately 18 Gm were then infected with the Ravenel strain of *M. tuberculosis* var. bovis by the standard method<sup>3</sup>. Two groups of 10 mice each were left as untreated controls, one group received 2 mg of aureomycin *per os* daily and one group 0.5 mg *per os* daily. As a positive control *p*-aminosalicylic acid incorporated in the diet was used in one group at 0.75 per cent and in the other at 0.375 per cent. As has been shown elsewhere<sup>3</sup>, the delay in the  $t_{50}$  (calculated time of survival of 50 per cent of the mice) has been shown to be a highly satisfactory, reproducible, and objective method of measuring antituberculous activity. Under the above circumstances, neither dose of aureomycin had any effect on the  $t_{50}$ , whereas *p*-aminosalicylic acid in the same experiment gave a delay of 7.2 days at the 0.75 per cent level and a delay of 4.5 days at the 0.375 per cent level. Although on a per kilogram basis the 2 mg daily dose represents approximately thirty-five times the dose given by Steenken and Wolinsky, it will be noted that even at this dose aureomycin *per os* had no detectable effect upon the course of infection with *M. tuberculosis* in the mouse.

THE DIVISION OF MICROBIOLOGY  
THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH  
NEW BRUNSWICK, NEW JERSEY  
APRIL 22, 1949

G. RAKE  
R. DONOVICK

<sup>1</sup> Steenken, W., Jr., and Wolinsky, E., *Am. Rev. Tuberc.*, 1949, 59, 221.

<sup>2</sup> Subsurface active agent incorporated in the medium at the suggestion of Dr. R. Dubos of the Rockefeller Institute for Medical Research.

<sup>3</sup> Rake, G., *et al.*, *Am. Rev. Tuberc.*, 1949, 60, 121.

## BOOKS

R A WILLIS *Pathology of Tumors* Pp xxvii, 992 Butterworth & Co , Ltd , London, England, The C V Mosby Company, St Louis, Mo , 1948 Price \$20 00

Doctor Willis' approach to the problem of the pathology of tumors is at the same time highly individual and honestly objective. His personal bias gives spice to the book. He has combined his own long and wide experience in the study of neoplasm with his broad knowledge of the writings and conclusions of other students of the field, but he has never let the latter sway his own judgment. He never defers to authority nor straddles a difference of opinion and yet his confidence in the correctness of his own views falls short of the didactic in almost every instance.

The volume is divided into two parts. The first, which comprises about a fifth of the whole, is concerned with a general discussion of neoplasia. It is well done and at the same time regrettably concise. It might well have been expanded into a full companion volume for the main body of the work. This Part I disposes quickly with the enigma of definition, logically discounts and discards all classifications but that one proposed by the author, touches the salients of the experimental production of tumors, deplores the defects of statistical analysis, briefly catalogues tumors of other species than man, and goes on to a discussion of growth, spread, metastasis, and the general nature of neoplasia. The condensation of this large body of knowledge and experimental endeavor into little more than two hundred pages is a feat remarkably and admirably contrived. From it a reader who is quite unfamiliar with the field is able to acquire a general background that is valuable either for itself alone or for more specific and detailed literary inquiry into special aspects of cancer study. As such it is of value and interest to students of medicine whether undergraduate or postgraduate.

Part II comprises the remaining four-fifths of the book. It is entirely unlike Part I in that its concern is a detailed and systematic description of the morphology, behavior, and incidence of the many individual tumors that arise in the mammalian body. It is a textbook for the advanced study of neoplasia and for the practicing surgical pathologist, and a reference book for the clinician who day by day encounters the distressingly common or the puzzlingly rare new growths.

One by one Doctor Willis considers in systematic detail the epithelial tumors of the organs or organ systems of the human body. The approach to each is much the same, and this is a praiseworthy uniformity which adds to the value of the book both as a reference work and as a pedagogical instrument. An example of this is the treatment of the "Epithelial Tumours of the Trachea, Bronchi, and Lung." Here, after a brief and semihistorical introductory paragraph dealing chiefly with pulmonary carcinoma comes a section on "Frequency, Age, Sex, Race and Species Incidence" which after a categorical discussion is followed by "Possible Causative Factors" again considered in detail and in turn followed by

the more morphological aspects of the lesions, "Site of Origin", "Growth, Complication and Local Spread", and "Metastasis" Bronchial adenomas and other benign tumors are treated in a sufficient manner at the end of the chapter

The adherence to this pattern of treatment of the various anatomical areas and their tumors tends unavoidably to monotony but this defect is offset by the facility to reference afforded by it The profusion of case histories of patients or specimens studied personally by the author, which he uses constantly throughout the text to illustrate his thesis, adds greatly to the individuality of the work and comfortingly confirms the reader in his opinion that he is perusing something by someone who has "been there" The interspersing of these case histories softens the effect of the reiterated personal pronoun, especially in the author's expression of opinion

The text is copiously and excellently illustrated with photomicrographs of rare tumors and of the less common aspects of familiar tumors Doctor Willis quite properly has not attempted to duplicate standard textbook reproductions

The bibliography at the end of each chapter is not only full and timely but has the almost unique virtue of presenting in bold face type those works which the author has thought for one good reason or another to be of outstanding value, and to each he has appended in parentheses his reason for so thinking Thus discrimination is added to completeness

JOHN M PEARCE

NEW YORK CITY

VICENTE SANCHIS-OLMOS *Skeletal Tuberculosis* Pp xiii, 261 Williams & Wilkins Co, Baltimore, Md, 1948 Price \$5 00

According to the preface, this book has been written "with the intention of emphasizing that which is new or little known" It is written by a Spanish orthopedic surgeon and is based on his experience and teaching in Spain, supplemented by observations made while he was in Boston as a graduate student in orthopedic surgery The author reviews the pathogenesis, the pathology, the roentgenologic examination, symptoms and their evolution, and the treatment A second part deals with special subjects

In discussing pathogenesis and pathology, the author goes into considerable detail about various types of tuberculous lesions, such as granular, exudative, and caseous synovitis and osteo-arthritis These undoubtedly exist, and the author may be correct in his statements about these and their practical significance Nevertheless this reviewer believes that the author fails to show convincing proof, in some of the roentgenograms exhibited as demonstrating granular osteitis and exudative synovitis, that they are such

There are actually some statements to which exception may be taken, such as "In other instances [spondylitis] it is the deformity [kyphosis] that first attracts attention" This is unfortunately true at times, but we believe that the diagnosis of tubercular spondylitis should be made before the deformity develops Again, in discussing pathologic dislocations, the author mentions two classes,



early and late The early one is said to be due to "a large intra-articular effusion that hastens the loss" Such a dislocation in a tubercular joint without some tissue destruction seems to the reviewer a very remote possibility

The book is valuable as a compilation of known facts regarding the incidence of tuberculous osseous lesions in a well-known institution in Spain As a basis for teaching the more theoretic phases of pathology and pathogenesis, it is worth while if it is realized that a considerable part of that portion of the book must be based on theory

R. K. GHORVLEY

RENÉ SAND, Professeur de Médecine Sociale à l'Université libre de Bruxelles  
*Vers la Médecine Sociale Pp 671, J-B Baillière et Fils, Paris, 1948*

From the point of view, historical-bibliographical rather than analytical-pathological, this book is a most valuable enrichment of present day literature on social medicine The wide scope of the materials covered is overwhelming, and the author's bibliographic knowledge is evidenced in each chapter starting as a rule with presentation and quotation from ancient history throughout the ages until most recent time Already the list of contents gives proof of it In individual chapters are treated the history of the medical professions, the history of hospitals, and the history of personal hygiene All of these and the subsequent accounts are accompanied by numerous quotations from Graeco-Roman, Chinese, Indian, Arabic, Middle Age, and Modern sources These are followed by chapters dealing with the history of public hygiene, epidemics, and public health, and the history of social hygiene The latter is divided into a good many subsections For example, on the first programs of social hygiene throughout the world, the role that single inspiring personalities played in the development of public health and city sanitation, such as Philippe Buchez in France, Salomon Neumann and Rudolf Virchow in Prussia, Max von Pettenkofer in Bavaria, is reviewed Subsequent sections in this long chapter deal with the coming of preventive medicine, marriage counseling, the care of pregnant mothers and their new born, school hygiene, physical health and periodical examinations of school children, and the fight against tuberculosis and other mass diseases Moreover such subjects as housing and urbanization, physical and hygienic education, and many more items of modern preventive medicine are covered Further chapters treat the history of factory work since antiquity, the protection of labor, legislation on work conditions and occupational injuries, the history of public assistance and social insurance, the history of the sciences of man, among which statistics, demography, anthropometry, social psychology, genetics, eugenics, and population politics are named and briefly annotated Finally, the book closes with a longer chapter considering in some detail, country by country, the present advancement of social medicine, its recent developments, achievements, and institutions A relatively large subsection in this chapter is devoted to social medicine in the English-speaking world, especially Great Britain and the United States, after the earlier developments in Germany and

France have been reported upon at some length. A few sections in this chapter also deal with the still controversial definitions, limitations, and methods of social medicine, and lastly with the teaching and curricula of this new branch at various universities and medical schools.

There certainly is a tremendous field of medical science and its relationship to social conditions covered in the book, and it is almost past belief that a single personality, even of such erudition and age-old experience as René Sand in various brackets of hygiene and public health, is able to master this vast field. Small wonder, then, that certain subjects, such as the control of tuberculosis, the fight against venereal diseases in its singular stages, the detection of cancer and its differential mortality, the explanations and applications of vital statistics, the importance of anthropometric evaluations, et cetera, are only sketchily dealt with. Nevertheless, the wealth of bibliographic footnotes is amazing everywhere. There are almost no statistical tables in the large book to characterize differential prevalence of diseases in different socio-economic or occupational groups. Evidently, as the title of the book, *Towards Social Medicine*, may indicate, the author's intention was to describe the trend of public health and group medicine since antiquity rather than to give a systematic social pathology at the present time by demonstrating the degree to which diseases are influenced (or not) by social-environmental conditions. The latter can be done only by careful presentation and analysis of pertinent statistics, the former (the trend of social medicine throughout history) is masterfully elucidated and amply supported by an abundance of bibliographic footnotes and appendix notes which in themselves make the book worth possessing as a source for further inquiries in the field of social medicine. There is at the end a supplementary bibliography on general subjects, an alphabetic index of names, and a carefully planned and useful index by countries and subjects treated in the book.

GEORGE WOLFF

WASHINGTON, D. C.

A. BRADFORD HILL *Principles of Medical Statistics* Fourth edition London, The Lancet Limited, 1948 Pp vi and 252 Price 7s 6d

This is the fourth (revised and enlarged) edition of the "Principles" after the third edition was reprinted three times during the war without essential changes, so great was the demand among medical circles for this little book on statistical treatment of medical problems. This in itself is a high recommendation of the book from the practical point of view. I have before me the first edition that appeared in 1937 and may well be in a position to compare the two as to their practical value. The book has increased from 171 pages in the first edition to 252 in the present without having lost its principal character of being a readable introduction to all who take time out to study a few fundamental statistical problems. A new chapter (The Average) has been added to demonstrate how central values (mean, median, mode) can be easily calculated from grouped figures (by using arbitrary units) without involving arithmetical hardships.

Such a chapter has a highly educational value for all who shrink from statistical computations. The further chapters on problems of sampling (Proportions, Differences, Discussion of the Chi-square test) have been retained for the larger part as they were printed in the former editions with some supplementary examples added. Special attention is given to the discussion of the statistical significance of differences which are of great importance in clinical research, as well as in public health work, to prove (or disprove), for instance, the value of a new therapeutic agent, the efficacy of a vaccination procedure, the variation of body measurements between groups of school children, et cetera. There are two chapters on the calculation, use, and misuse of the correlation coefficient, similarly as in the first edition. The chapter on life tables, which was somewhat sketchy in the former editions, has been essentially enlarged and illustrated by examples, emphasizing the great importance of survival rates and other life table values (life expectancy) in vital statistics and population theory. Of special value, it seems to the reviewer, are the following three chapters on fallacies and difficulties in the use of vital statistics. Here it may be mentioned that the so-called proportional death rates (proportion of specific deaths among all deaths) are critically viewed. These ratios are too often used (because they are readily obtainable) instead of the death rates proper in a population at risk. Tuberculosis is chosen as an example to show that such proportion (though arithmetically correct) is never a good measure for the risk of dying from tuberculosis, for it depends just as much on the relative frequency of *other* causes of death, the increase or decrease of which must necessarily influence the proportion of tuberculosis deaths. The same criticism is applied to the use or misuse of crude and standardized death rates, two new chapters are added to discuss the standardization methods usually employed. It is obvious that the death rate in a chosen standard population is a fictitious rate for the risk in a given population, but it will be of great value as a comparative index in populations of different age and sex composition and, in the United States in particular, of different race composition. In such cases, the overall (or crude) rate gives a distorted picture. The direct and indirect methods of standardization are shown in special examples.

There is no doubt that Hill's "Principles," though somewhat more technical in the new edition, will gain more friends in medical circles. There are quite a few mathematical-statistical textbooks crowded with formulas and derivations from abstract examples on the market, but there is hardly a better guide available to the public health worker and physician for statistics applied to medical problems. The work is critical without being sophisticated. In his introductory chapter the author states quite ably "No statistical method can compensate for a badly planned experiment," in public health, however, we have to deal as a rule "with statistics that come from no deliberate experiment but that arise, and are collected, from a population living and dying in an everyday course of events." To analyze these "mass experiments," which cannot be planned a priori, a good deal of knowledge in the subject matter is necessary, in addition to statistical methods, to make the statistical analysis a live contribution to research.

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# THE AMERICAN REVIEW OF TUBERCULOSIS

## ABSTRACTS

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### CLINICAL STUDIES, TUBERCULOSIS

**Dangers of Vitamin D<sub>2</sub> Therapy**—Although previous good results warrant the use of large doses of vitamin D<sub>2</sub> in certain forms of tuberculosis, this treatment is not without danger. Pathologically the lesions produced by this treatment are identical with those seen after the administration of irradiated ergosterol. There is calcification of the large vessels of the lungs, the heart, the dura, the digestive tract, and of the kidneys. The damage is particularly severe in the kidneys where calcifications have been observed in the renal epithelium, the interstitial tissue, the glomeruli, and the arterioles. Clinically, intoxication is usually manifested by gastro-intestinal symptoms but it is noteworthy that severe kidney damage may precede clinical signs. This is especially true in kidneys which have been damaged by tuberculosis. Elevation of the blood urea nitrogen is an early danger signal and is observed in most patients with renal tuberculosis. This azotemia usually persists after the treatment is stopped. Elevation of the blood calcium and phosphorus is observed less frequently. The dosage of vitamin D<sub>2</sub> is 15 mg once or twice a week and is continued as long as it is tolerated. This is rarely more than five or six weeks in patients with renal tuberculosis.—*Des accidents de la vitamino-thérapie D<sub>2</sub> a fortes doses, en particulier dans la tuberculose renale*, M Secrétan, *Schweiz med Wchnschr*, January 24, 1948, 78:49.—(H Marcus)

**Pneumothorax for Minimal Tuberculosis**—Statistics from a French sanatorium for high school and college students between the ages of 15 and 20 show that an increasing number

of the cases are being diagnosed by routine examination, 20 per cent in 1945 and 48 per cent in 1947. During 1947, only 14 per cent of the patients had far advanced tuberculosis, most had well localized, small infiltrations with or without cavitation. Of the 145 patients discharged from the sanatorium since its opening in 1945, 121 had been treated with pneumothorax and 81 per cent of these had favorable results. Only 57 per cent of the 33 patients treated with a simple sanatorium regimen responded favorably. The maximum observation period for any case was 25 years. There were 40 asymptomatic patients with minimal lesions on the roentgenogram but without tubercle bacilli in the sputum. Sixteen of them were treated with pneumothorax and 24 with rest alone. After 30 months, 8 relapses had occurred in the conservatively treated group. None of the 16 patients with pneumothorax relapsed during that period and all were able to resume an increasingly active mode of life.—*À propos des indications du pneumothorax dans les formes bénignes de la tuberculose pulmonaire, (une statistique du sanatorium des lycéens et collégiens à Neuf-Moutiers-en-Brie)*, J Lardanchet, *Rev de la tuberc*, 1948, 12:845.—(V Lertes)

**Extrascapular Pneumothorax**—Cavities which have remained open under a thoracoplasty can be collapsed by an extrascapular pneumothorax. An extrascapular pneumothorax also has the advantage of preventing paradoxical breathing which is frequently seen after thoracoplasty. In the 20 patients reported by the author an extrascapular pneumothorax was established following a second stage thoracoplasty.—*Die extrascapulare Luftfüllung nach*

Obergeschossplastik, *K Janauschek, Wien klin Wchnschr, December 24, 1948, 60 825* — (G C Leiner)

**Decortication and Lobectomy** — The results of thoracoplasty have been disappointing when pulmonary tuberculosis was uncontrolled by pneumothorax and complicated by tuberculous empyema or an unexpandable lung. The Schede or Keller operations with resection of the parietal pleura have been the best available surgical treatment in the past. However, the incidence of cavity closure and healing of the empyema has been low and the degree of mutilation and disfiguration of the patient often severe with these procedures. A new, combined procedure is suggested for selected cases. It consists of lobectomy when the tuberculosis is confined to one lobe with decortication of the remaining lobe or lobes. Two illustrative cases of upper lobe tuberculosis, uncontrolled by pneumothorax, are presented. In neither case could the lung be re-expanded and in neither case was it thought that thoracoplasty over the unsuccessful pneumothorax would produce a satisfactory collapse. One case was further complicated by a mild tuberculous empyema. Each was treated successfully by lobectomy with extrapleural dissection and decortication of the remaining lung tissue. In both instances streptomycin and penicillin were given parenterally for one week before and for three weeks following the operation. Lobectomy, with decortication if necessary, should be considered when a pneumothorax has been unsuccessful in obtaining cavity closure despite a seemingly adequate anatomical collapse of the diseased lobe which re-expands slowly. This would avoid the risk of spreading the disease during a prolonged period of re-expansion before thoracoplasty. — *Decortication and lobectomy for uncontrolled pulmonary tuberculosis with tuberculous empyema or unexpandable lung, I A Sarot, Quart Bull, Sea View Hosp, April, 1948, 10 47* — (K T Brd)

**Hemothorax after Pneumonolysis** — It is recommended that the blood be removed from

a hemothorax which has developed following a pneumonolysis. This was done by thoracotomy in 11 cases. The operation should be performed within eight to fourteen days after the pneumonolysis, as soon as the temperature has become normal. — *Die operative Ausräumung der vollgebluteten Pneumolyse, K Janauschek, Wien klin Wchnschr, October 22, 1948, 60 680* — (G C Leiner)

#### CLINICAL STUDIES, NONTUBERCULOUS DISEASES

**Boeck's Sarcoid** — The pathological observations in 4 cases of Boeck's disease showed lesions which resembled one another in many respects in the acute as well as in the healing stages despite the varied clinical courses. Although complete regression may occur, fibrosis and hyalinization without calcification were seen in all 4 cases. In the acute stage there was a predominance of histiocytes occurring in discrete tubercles without many lymphocytes and without necrosis. In the healing and healed stages fibrosis, a tendency toward hyalinization within uncalcified tubercles, and the occasional retention of outlines of the tubercles in hyalinized areas, are suggestive of Boeck's disease. — *Boeck's disease, Rosenthal, J, & Feigin, I, Arch Path, June, 1948, 45 681* — (E Bogen)

**Paradoxical Mediastinal Swing in Pleurisy** — The occurrence of mediastinal shifting or Holzknecht-Jacobson's sign in some cases of bronchial obstruction is well known. It has been reported occasionally as the sole indication of an obstruction later demonstrated by bronchoscopy. The phenomenon consists of a shifting of the mediastinum toward the affected side during inspiration, particularly deep inspiration, and a return to or beyond its former position during expiration, especially following a cough. The respiratory immobility of the affected lung, which neither completely fills on inspiration nor is completely emptied on expiration, produces the shifting of the mediastinum. The expanded sound lung exerts pressure and the incompletely filled hemothorax on the affected side acts as

an attracting force Atelectasis or emphysema are not necessarily factors In certain cases of pleurisy, the authors have noted a paradoxical mediastinal shifting toward the sound side, and report 4 cases in which it occurred In all of them there was complete immobility of the affected side of the thorax including the diaphragm and the shifting occurred when the sound lung emptied rapidly following a cough—*Le balancement médiastinal de sens paradoxal dans certaines symphyses pleurales et le signe d'Holzkecht-Jacobson*, M Lévrat & G Desperres, *Le Poumon*, July-August, 1948, 4 209—(A T Laird)

**Pedicles of Upper Lobes**—The anatomical relations of the arteries, veins, and bronchus which make up the stem of the upper lobe of the lung are of especial interest to the surgeon during a lobectomy According to the newer technique the use of the tourniquet has been abandoned, the vessels are ligated separately, and the bronchus is closed by suturing The authors report anatomical studies made on the cadaver and during the course of the removal of 16 upper lobes The pedicles of the right and left upper lobe differ because of the presence of the lingula on the left and the passage of the left branch of the pulmonary artery around the left upper lobe bronchus The right upper lobe bronchus usually arises from the outer wall of the main bronchus about 21 mm from the tracheal bifurcation Anomalies in its origin are comparatively rare though it has been found to start directly from the trachea or to leave the main bronchus in a common trunk with the branch to the middle lobe The course of the bronchus is outward and upward to the upper lobe, where it may terminate in 2, 3 or 4 branches The upper lobe of the right lung always receives several arterial branches including the principal or anterior artery, the accessory or retrobronchial artery and, rather frequently, other important branches These may not be seen unless the pedicle is examined by way of the interlobar fissure The most important of the veins is the posterior vein of the upper

lobe In the left lung, the upper lobe bronchus comes off the main bronchus farther from the bifurcation of the trachea than on the right side It is often not more than 15 mm in length but is considered long enough to suture The bronchus terminates in an ascending and a descending branch The left main branch of the pulmonary artery is smaller in caliber than the right and the arrangement of its subdivisions is variable Approach by way of the interlobar fissure is necessary to locate some of them The left superior pulmonary vein consists entirely of branches derived from the upper lobe Variations in the origin of arterial and venous branches occur on both sides—*Les pédicules des lobes pulmonaires supérieurs*, A Maurer & F Tobé, *Le Poumon*, January-February, 1948, 4 7—(A T Laird)

**Technique of Upper Lobe Lobectomy**—This paper is a discussion of the removal of the upper lobe by dissection and severing of the elements of the pedicle as practiced by the authors in a series of 16 lobectomies Their series included removal of the right upper lobe in 8 cases, of the right upper and middle lobe in 3, and of the left upper lobe in 5 They were undertaken for an abscess of the lung in 9 cases, for cysts of the lung in 5 cases, and once each for cancer, tuberculosis, and bronchiectasis The feature of the operation to which the authors call special attention is the ligation of each of the blood vessels in the pedicle with the closure of the bronchus by sutures The patient was placed in the lateral position and general anesthesia, usually cyclopropane-oxygen-curare, with tracheal intubation was employed The incision was made along the fifth rib or in the fifth interspace, in adults the fifth rib was removed by subperiosteal resection The principal artery and the veins of the right upper lobe were reached from the front The other arteries of the right upper lobe were approached by way of the interlobar fissure which in some cases had to be reconstituted The bronchus was finally attacked from the fissure or from its posterior aspect In most cases it could

be sutured directly without preliminary closure of any branches. The method of Sweet was followed, the bronchus being clamped on the pulmonary side and then sectioned and sutured progressively. Pleuralization of the bronchial stump on the right side was accomplished by utilizing the posterior mediastinal pleura which was made to cover the anterior surface of the bronchus. In the left lung the aortic pleura was used. It was always necessary, especially in cases of abscess or tuberculosis, to prevent the escape of secretions from the upper lobe bronchus before the bronchus was sutured. Otherwise they might have been aspirated into the other lung or into the lower lobes of the same lung. The authors preferred previous preparation of the patient, tracheal aspiration and minimal pulmonary manipulation rather than the use of an obturator or clamp. Aseptic lesions without bleeding pleural surfaces do not require drainage but infected cases may need long-continued aspiration. Of the 16 patients who were operated upon, 3 have died: one of tuberculous meningitis after the removal of an upper lobe for tuberculosis and 2 of pulmonary abscesses. In 4 cases a bronchial fistula developed—*Technique de la lobectomie supérieure par dissection des éléments du pédicule*, A Maurer & J Mathey, *Le Poumon*, January-February, 1948, 4 21—(A T Laird).

**Relative Safety of Upper Lobe Lobectomy**  
—A study of 63 cases in which an upper lobe of the lung was removed shows that the results of this operation are as satisfactory as those following other pulmonary resections. This series, operated on at the Massachusetts General Hospital in Boston from 1943 to 1946, included 45 cases in which the upper lobe alone was removed, 18 in which the upper lobe and some other portion of the lung were resected, 16 in which the middle lobe alone was removed, one in which the apical portion of the lower lobe, and one in which the middle lobe, and a portion of the lower lobe were removed. In the series there were 13 cases of lung abscess, 21 of tuber-

culosis, 12 of cancer, 10 of bronchiectasis, 3 of pulmonary cysts, 2 of chronic pneumonia, and 2 of benign tumors. In all of the cases, the blood vessels in the pedicle of the lobe were ligated separately, the bronchus was divided and sutured, and the stump was pleuralized. Prophylactic penicillin therapy was given for several days before the operation, transfusions and plasma infusions were given during the procedure. Drainage was employed after resections for tumors or suppurative lesions; of the 63 cases, 45 were drained. Lobectomies for abscess or tuberculosis are attended by considerable risk as are those in febrile patients and in cases where more than one lobe must be removed. The conditions of the pleura, the amount of expectoration, and the necessity for drainage also influence the outcome. The prognosis is improved by the use of adequate preoperative preparation of the patient, simple operative procedures with as little trauma as possible, excellent anesthesia, periodic re-expansion of the lung during the operation, careful closure of the bronchial stump, airtight drainage, and careful post-operative care. In this series of 63 resections of an upper lobe, there was immediate re-expansion of the remaining lobes and an uneventful convalescence in 30 cases (47.6 per cent) and delayed re-expansion in 33. Among the latter, were 15 cases of pleural effusion and 18 cases of bronchial obstruction. There was no re-expansion in 8 cases (11.1 per cent) with subsequent serious complications. There were 5 deaths (8 per cent mortality). These results are comparable to those in a series of 99 resections of lower lobes performed at the same hospital during the same period. There was immediate re-expansion and prompt recovery in 41 cases (41.1 per cent). There were serious complications in 11 cases (11.1 per cent) and 5 patients died (5.1 per cent mortality). It thus seems that removal of an upper lobe of the lung is about as safe as removal of a lower lobe if the proper personnel and facilities are available—*La lobectomie supérieure*, R H Sweet & H LeBrigand, *Le Poumon*, January-February, 1948, 4 46—(A T Laird).

**Bronchial Adenoma**—The clinical course of bronchial adenoma can be divided into three distinct phases (1) Phase of hemoptysis Other symptoms are lacking at this time and, because of the bleeding, a mistaken diagnosis of tuberculosis is sometimes made (2) Phase of bronchial stenosis Recurrent attacks of pneumonitis, often associated with pleural effusion, frequently lead again to a diagnosis of tuberculosis at this stage (3) Phase of suppurative pneumonia and atelectasis The most important diagnostic procedure is bronchoscopy although some help may be derived from roentgenographic studies that include bronchograms and planograms If the patient is seen early, especially in the first phase of the illness, removal of the tumor through the bronchoscope should be attempted This is not usually possible in the second phase, and in the third phase only lobectomy or pneumonectomy is curative Other indications for excisional surgery are the impossibility of removing the tumor through the bronchoscope, extraordinarily great vascularity of the tumor, and severe suppurative disease with bronchiectasis or abscess formation distal to the tumor—*Das Krankheitsbild und die Differentialdiagnose des Bronchialadenoms, A Kappert, Schweiz med Wchnschr, January 17, 1948, 78 26*—(M Marcus)

**Tumor Cells in Sputum**—The value of microscopic examination of the sputum for tumor cells is illustrated by 3 case reports All 3 patients were suspected of having pulmonary tuberculosis but sputum studies revealed the correct diagnosis of primary pulmonary carcinoma—*Apical pulmonary carcinoma and tuberculosis The value of sputum cell study in the differential diagnosis, M Bergman, B A Shatz & I J Flance, J A M A, November 13, 1948, 138 798*—(H Abeles)

**Bronchial Washings**—Bronchial washings according to the technique of Manoel de Abreu were performed on 257 patients Demonstration of tubercle bacilli in the speci-

mens obtained was attempted only by culture or guinea pig inoculation A comparison between the results of gastric and bronchial lavage was carried out on 150 cases with roentgenographic changes suspicious for tuberculosis The patients had no expectoration or sputa without demonstrable tubercle bacilli Bacteriological evidence of tuberculosis was found in 47.2 per cent of these cases, in 22.4 per cent by both gastric and bronchial lavage, in 20 per cent by bronchial washings only, and in 4.8 per cent by gastric washings only In 107 persons with roentgenographic changes of undetermined origin and sputum without tubercle bacilli, bronchial washings revealed the bacilli intermittently in 41.1 per cent Among 90 persons in whom routine roentgenograms showed apparently fibrotic changes, 35 per cent had tubercle bacilli demonstrable intermittently with this method Bronchial washings are of special interest in determining the length of pneumothorax treatment and in evaluating the results of collapse therapy—*La recherche du bacille tuberculeux par le lavage pulmonaire, Ch Gernez-Rieux, A Breton & A Sevin, Rev de la tuberc, 1948, 12 743*—(V Lentes)

**Sarcoidosis**—This case report traces the evolution of Boeck's sarcoid over a period of ten years to its termination in miliary tuberculosis A 27 year old male patient was under the supervision of the tuberculosis control division of his home town for ten years There was persistent hilar adenopathy demonstrable roentgenographically, with a negative tuberculin reaction No biopsy was possible because of absence of peripheral lymph node enlargement During the period of observation the patient remained in good health and was able to work He developed miliary tuberculosis without meningitis after ten years observation His tuberculin test became positive and his disease was rapidly fatal Autopsy showed many hematogenous tuberculous lesions throughout the viscera The paratracheal, paraesophageal and abdominal lymph nodes showed very extensive hyaline changes with epithelioid cells and



Langhans giant cells. The connective tissue was so dense that it replaced the normal architecture of most lymph nodes entirely. Although there was fresh cavitation in some of the nodes at the bifurcation of the trachea, the nodular hyalinization of most of the lymph nodes was characteristic of long standing sarcoidosis. In addition to these findings, there was fresh tuberculous spondylitis of the second dorsal vertebra.—*Morbus Besnier-Bocch mit Uebergang in Milchartuberculose*, Jenny Müller & A. Pedrazzini, *Schweiz med Wchnschr*, February 14, 1948, 78:126—(M. Marcus)

#### ANTIMICROBIAL THERAPY

**Streptomycin Resistance**—A series of 13 cases of pulmonary tuberculosis was treated with streptomycin. The patients ranged from 15 to 30 years of age and were suffering from acute progressive bilateral tuberculosis of recent origin. All had cavities. Streptomycin was given in doses of 0.5 Gm. every six hours intramuscularly for six months to some of the group and for four months to the remainder, the observation period was six months. All the strains of tubercle bacilli obtained prior to treatment were either half as sensitive to streptomycin as the control strain of H37Rv, twice as sensitive, or equal in sensitivity, with one exception. The bacilli from 12 of the 13 cases showed increased resistance to streptomycin after treatment and 11 of these strains were 32 or more times as resistant as the control strain. In most cases the resistance of the bacilli increased rapidly and then remained about the same. Two-thirds of the patients developed resistant bacilli within 48 days. There was a definite relation between the clinical progress before resistant organisms appeared and the degree of resistance that eventually occurred. The patients doing well in the early stages of treatment had bacilli which developed a low degree of resistance, while those patients doing poorly later produced more highly resistant organisms. The higher the degree of resistance, the more rapidly it appeared. There

was no significant correlation between the median day that resistant bacilli appeared or the degree of resistance that developed and the clinical progress of the patient after that development. Nor was there any demonstrable relation between the time at which resistant strains developed and the general condition of the patient on admission. There was no relationship between the degree of resistance and the extent of cavitation. There are two possible mechanisms by which strains of tubercle bacilli resistant to streptomycin might appear in the sputum: (1) the entire surviving bacterial population might become gradually adapted to growth in the presence of the drug, or (2) the patient's population of tubercle bacilli before treatment with streptomycin might contain organisms with varying degrees of resistance, the more highly resistant being few in number but under treatment having an advantage over the sensitive strains and gradually replacing them.—*Streptomycin resistance in pulmonary tuberculosis*, J. Crofton & D. A. Mitchison, *Brit. M. J.*, December 11, 1948, 4588:1009—(R. W. Clarke)

**Changes in Meningitis after Streptomycin**—The pathological observations in 10 children who had been treated with streptomycin for tuberculous meningitis are reviewed. The exudative process showed a tendency to organize and form gradually sclerosing scar tissue. The proliferative processes, such as miliary tubercles, were encapsulated by connective tissue; early miliary tubercles were transformed into connective tissue. Hyalinization and calcification were seen also. These changes, which are signs of healing in a pathological sense, were the causes of late complications such as internal hydrocephalus and obliterating endarteritis resulting in encephalomalacia; rare late complications were tuberculoma and lymphocytic encephalitis.—*Pathologisch-anatomische Befunde bei mit Streptomycin behandelten Fällen von Meningitis tuberculosa*, H. Chiari, *Wien klin Wchnschr*, December 31, 1948, 60:837—(G. C. Leiner)

**Therapy of Meningitis in Children**—The dosage of streptomycin in the treatment of tuberculous meningitis in children has been modified in an attempt to avoid the high dosage recommended by Hinshaw and Feldman and to improve on the small and only moderately effective dosage of Cocchi. The following schedule has proved very successful: first month of treatment, 500 to 1,000 mg of streptomycin daily intramuscularly and 1 mg per Kg of body weight daily intrathecally; second month, same intramuscular schedule but an intrathecal injection only every other day; third month, same intramuscular dosage with intrathecal treatment only about twice a week depending somewhat on the changes in the cerebrospinal fluid. At the same time 1.5 to 3 Gm of Promin is given daily intravenously and once a month a massive dose of vitamins A and D is administered. Early diagnosis and early treatment are the most important conditions for success. Treatment of other bacterial forms of meningitis is also discussed in this paper—*Der heutige Stand der Meningitis-Therapie im Kindesalter*, G Fanconi, *Schweiz med Wchnschr*, February 14, 1948, 78:121—(H Marcus)

**Streptomycin for Tuberculous Pericarditis**—A 17 year old male Negro who had acute tuberculous pericarditis with effusion, tuberculosis of the left lower lobe, and tuberculous lymphadenitis was treated with streptomycin. The pericarditis responded very favorably to the treatment—*Streptomycin in acute tuberculous pericarditis, a case report*, H C Meredith, Jr, *Am Heart J*, January, 1949, 37:129—(G C Leiner)

**Streptomycin for Miliary Tuberculosis**—Streptomycin has been used to treat children with disseminated tuberculosis. Of 9 children with miliary pulmonary tuberculosis, 5 were discharged and are well, 4 are still under treatment. Of 44 children with tuberculous meningitis, 11 were discharged and are well, 5 are ready to be discharged, 12 are still under treatment, and 16 have died. Of 2 children with miliary peritonitis, one was dis-

charged and is well, one is being treated and is improving. Of 7 infants with tuberculosis without miliary dissemination, one died but 6 improved—*Streptomycinbehandlung der miharen Tuberkulose*, O Ruzicka, *Wien Klin Wchnschr*, December 31, 1948, 60:840—(G C Leiner)

**Fundi during Streptomycin Therapy**—The eye-grounds of 42 children were examined repeatedly during streptomycin treatment for tuberculous meningitis or miliary pulmonary tuberculosis. In more than one-third of the cases, changes of the papilla were observed, in more than one-third, changes of the choroid, multiple miliary tubercles, or solitary tubercles, were seen. In most cases, there was a quick regression of these foci soon after treatment with streptomycin was begun. In cases which showed slow regression of these foci, complications and relapses occurred. No evidence of any toxic effect of streptomycin on the optic nerve was seen—*Augenhintergrundsbefunde bei der Streptomycinbehandlung der Meningitis tuberculosa unter der miharen Lungentuberkulose*, F Meyer, *Wien klin Wchnschr*, December 31, 1948, 60:842—(G C Leiner)

**Otolaryngological Tuberculosis**—A group of 20 cases of laryngeal tuberculosis, associated with pulmonary tuberculosis, was treated with parenteral streptomycin. Involvement of the epiglottis, aryepiglottic folds, and arytenoids was found in 45 per cent of this group so that dysphagia and hoarseness were predominant symptoms. Streptomycin was given in a dosage of 2.0 Gm daily for one week followed by 1.0 Gm daily for 83 days. Blood levels frequently were 20 to 40  $\gamma$  per cc of serum during the first week, thereafter the levels were between 5 to 10  $\gamma$  per cc of serum. Upon completion of therapy, 14 showed a "healed larynx," a fibrotic end stage with no evidence of activity, 4 showed an "almost healed larynx," fibrosis, except for a small area of injection or some other slight involvement, the remaining 2 showed improvement. An average of 21 days of treatment

was required before subjective and objective evidence of improvement was noted. It required sixteen weeks for healing to occur. Of the 20 cases, 11 had vertigo at some time during treatment. Compensation with diminution or disappearance of vertigo occurred in every instance, despite an average age of 46.7 years. Streptomycin should be used for moderate or advanced tuberculosis of the larynx regardless of the status of the lungs. Nine cases of tuberculous otitis media and mastoiditis were treated with streptomycin but no definite conclusions could be drawn from this series. Some cases of tuberculous otitis media alone were healed by the use of streptomycin. In tuberculous mastoiditis, surgery is still indicated although streptomycin is a valuable adjuvant—*Streptomycin therapy in otolaryngologic tuberculosis*, J G Gilbert, J S Aronoff & D M Rosen, *Quart Bull*, Sea View Hosp, January, 1948, 103—(K T Bird)

**Streptomycin for Tuberculosis**—Twenty-six patients with far advanced bilateral pulmonary tuberculosis, whose disease was too acute or too extensive for routine collapse measures, were treated with streptomycin. In 24 patients sufficient improvement occurred to permit some form of collapse therapy. Streptomycin should never be used in a therapeutic test or during a period of observation of a patient for whom other treatment may be required. There is great danger in using streptomycin too early, since its effectiveness may be lost at a time it is most needed. Streptomycin treatment should not be instituted until a definite plan for the treatment of the patient has been worked out. In this group of patients streptomycin was used to prepare the patients for collapse therapy, that is, as an adjunct and not for complete cure—*Streptomycin as adjunct in treatment of acute pulmonary tuberculosis*, E R Levine, W S Klein & A Forman, *J A M A*, November 13, 1948, 138:808—(H Abeles)

**Streptomycin Stomatitis**—Severe stomatitis was observed in 3 patients during the course of intramuscular streptomycin treatment. The stomatitis disappeared promptly after discontinuance of the streptomycin treatment—*Stomatitis due to streptomycin*, H Beham & H Perr, *J A M A*, October 16, 1948, 138:495—(H Abeles)

**Penicillin Dust Inhalation**—An apparatus is described for the use of penicillin dust for infections of the respiratory tract. Three hundred and fifty-seven patients were treated with 100,000 units of penicillin dust one to three times a day. Allergic reactions were observed in 3 per cent of the patients after contact dermatitis was prevented by creaming the face. Maximum levels of penicillin in the blood were obtained one hour after inhalation. The best results were seen in the treatment of bronchiectasis—*Inhalation of penicillin dust*, L Krasno, M Karp & P S Rhoads, *J A M A*, October 2, 1948, 138:844—(H Abeles)

#### LABORATORY STUDIES

**Sputum Concentration**—A method is described for concentrating sputum prior to its inoculation into guinea pigs. (1) The sputum is liquified by incubation for twenty-four hours. The vitality of the tubercle bacilli is not impaired as it is by treatment with sodium hydroxide. (2) After dilution with ten times its volume of distilled water, the sputum is centrifuged. (3) The sediment is neutralized and 6 drops of penicillin G (5,000 units per cc) are added to control contamination. Inoculation is easy with this preparation—*Homogénéisation des crachats et centrifugation du bacille de Koch vivant en vue de l'inoculation au cobaye*, F Tison, *Ann Inst Pasteur*, February, 1948, 74:128—(V Leites)

**Cultures in Dubos Medium**—Dubos liquid medium was inoculated with suspensions of 0.1 to 0.01 mg of bovine or human tubercle bacilli. Growth was observed as a sediment

on and after the fifth day. The cultures rarely produced a homogeneous clouding of the fluid. No cultures could be obtained by inoculating the medium with organs from tuberculous guinea pigs—*Éssais de culture de BK dan le mihcu de Dubos, J. Valtis, F. van Deinsc & J. Solomades, Ann. Inst. Pasteur, February, 1948, 74 434*—(V. Leites)

**Laboratory Diagnosis of Tuberculosis**—No certain diagnosis of active tuberculosis can be made by roentgenography alone, tubercle bacilli must also be recovered from the patient's sputum or body fluids. Tubercle bacilli can be demonstrated more regularly by selecting caseous flecks in the sputum than by concentration methods. Small numbers of tubercle bacilli can be more readily detected by culture than by smear. Acid fast saprophytes cannot be differentiated from virulent tubercle bacilli on stained smears, but competent bacteriologists can distinguish, with considerable accuracy, pathogenic from non-pathogenic acid-fast bacilli on the Lowenstein-Jensen egg medium. In its present form the Dubos Tween-albumin liquid medium is not recommended for primary isolation. Urine and gastric contents frequently contain non-pathogenic acid fast bacteria, for this reason, guinea pig inoculation should be practiced on such specimens—*The laboratory diagnosis of tuberculosis, M. M. Cummings, Am. J. Pub. Health, March, 1949, 39 361*—(Max B. Lurie)

**Fluorescent Method for Smears**—A comparison was made between the results obtained with the fluorescent technique of Richards and Miller and those obtained with Pottenger's method for the Ziehl-Neelsen staining of sputum and gastric contents for tubercle bacilli. Of 280 direct smears of sputum stained by the Ziehl-Neelsen method, 148 (52.8 per cent) were found to contain acid-fast bacilli. The same number of direct smears from the same patients, when stained and examined by the fluorescent method, yielded 154 (55.0 per cent) positive smears. Concentrates of these 280 sputa yielded 186

(66.1 per cent) positive smears by the Ziehl-Neelsen method and 190 (67.8 per cent) positive examinations by the fluorescent method. In another series of 514 sputum concentrates, 347 (67.5 per cent) were found to be positive by the Ziehl-Neelsen method and 354 (68.4 per cent) by the fluorescent technique. Of 210 gastric concentrates, 89 (42.3 per cent) were positive by the Ziehl-Neelsen method and 108 (51.9 per cent) were positive by the fluorescent method. These figures show a higher percentage of positive examinations with the fluorescent technique. However, there are certain disadvantages to the use of this method. For best results a dark room is preferable. There are organisms other than *M. tuberculosis* which give fluorescence. Of 25 gastric concentrates found positive only by the fluorescent method, 11 were confirmed by guinea pig inoculation. This discrepancy is probably due to the presence of avirulent or nonviable tubercle bacilli or saprophytic acid-fast bacilli in the gastric contents and sputum. The possibility of finding acid-fast saprophytic bacilli is even greater in stools and urine. In addition, the likelihood of error in diagnosis is increased by any particles which have retained the auramine dye and so may be mistaken for bacteria. Of 63 samples of gastric contents in which one to three bacilli per slide were found after a careful search, 59 were positive when tested by inoculation. It may therefore be concluded that positive results obtained by the Ziehl-Neelsen method are of greater value than those obtained by the fluorescent technique and correlate better with the clinical condition of the patient. On the other hand, negative results by the fluorescent method are of great value. The results with this method may be improved by refinements in technique—*La microscopía fluorescente en la investigación del microorganismo tuberculosis, A. Gómez Muriel, Rev. mex. de tuberc., May-June, 1948, 9 81*—(F. Pérez-Pina)

**Effect of Chick Embryo Extract on Tubercle Bacilli**—It has recently been shown that the minced tissue of chick embryos facilitates the

growth of tubercle bacilli in synthetic media. The present publication describes the effect of this extract on the rate of growth, morphology and virulence of tubercle bacilli cultivated in the media recently developed by Dubos and Middlebrook. The extract (CEE) was made from 11 day old chick embryos and most of the experiments were carried out with human strains of tubercle bacilli, H37R<sub>1</sub> (avirulent) and H37R<sub>1</sub> (virulent). From 0.5 to 1.0 per cent of CEE definitely enhanced the growth of tubercle bacilli in the base medium to which oleic acid had been added. It was also noted that the maximum yield of bacillary growth was reached earlier with the extract than without. The addition of CEE to the oleic acid medium caused the bacilli to organize themselves in serpentine cords which were longer and more dense than those formed in the absence of the extract. The virulent variants normally grow in irregular clumps. A more striking effect was observed when Tween 80 was added to the base medium. The lipase present in CEE destroyed the Tween 80 and prevented the latter from inhibiting cord formation when virulent strains of bacilli were used. This unspecific effect was fundamentally different from the one obtained when oleic acid was employed. Inoculation experiments with Swiss albino mice seem to indicate that the virulence of H37R<sub>1</sub> was slightly increased following cultivation on a medium containing CEE. However, the extract did not confer virulence on the avirulent variant. Extracts prepared from rabbit testicles, from mouse brain, liver and spleen, from leukocytes of man and rabbits, guinea pigs and mice, and from egg yolk failed to show any effect on cord formation although they had some enhancing effect on the growth rate of tubercle bacilli—*The effect of chick embryo extract on the growth and morphology of tubercle bacilli*, Hubert Bloch, *J Exper Med*, September 1, 1948, 88 355—(J S Woolley)

**Sphingomyelin and Growth of Tubercle Bacilli**—In addition to certain long chain fatty acids available as Tween 60, Tween 80,

et cetera, there exist other lipids, of tissue origin, which have been shown to enhance the growth of tubercle bacilli. The growth-promoting effect of various sphingomyelins, cerebrosins and phrenosin was studied by adding them to a basal asparagine medium similar to the author's original medium. Their effect on the growth of small numbers of tubercle bacilli (H37R<sub>1</sub>) was studied when the nonionic wetting agent Triton 120 was used instead of Tween 80. The former is a heat-stable aryl-alkyl polyether of phenol which disperses the cultures without increasing the growth. All the preparations of sphingomyelin from kidney, liver, brain and lung proved almost as effective as serum albumin in enhancing the yield of bacilli. The cerebrosides and the phrenosin, on the other hand, decreased the ability of the medium to support the growth of small inocula. The wetting agent Triton A20 increased the yield through its dispersing effect on the lipids. The neutralizing effect of sphingomyelin on the toxicity of long chain fatty acids was similar to that of serum albumin. Sphingomyelin is a diamminophospholipid in which lignoceric acid is combined in amide linkage with the base sphingosine, phosphocholine being esterified to the latter. Lignoceric acid and its amide also enhanced growth, sphingosine did not. Sphingomyelin, like serum albumin, protects the bacilli against the toxic effects of long chain fatty acids and also supplies a water-dispersible source of lignoceric acid which is available for metabolic utilization—*The effect of sphingomyelin on the growth of tubercle bacilli*, R J Dubos, *J Exper Med*, July 1, 1948, 88 73—(J S Woolley)

**Wetting Agents and Growth of Tubercle Bacilli**—It is possible to obtain finely dispersed, submerged growth of tubercle bacilli by adding to the medium certain nonionic wetting agents. The polyoxyethylene esters of oleic acid (Tween 80, Tween 40, et cetera) have proved especially effective in this respect. Unfortunately, the ester linkage in these wetting agents is susceptible to enzymatic hydrolysis by lipases, a fact which prohibits

their use in media containing animal tissues or fluid rich in these enzymes. What is needed is a wetting agent capable of promoting dispersed growth of tubercle bacilli yet stable in the presence of animal tissues. Triton A20, an arylalkyl polyether of phenol, in some respects fulfills these requirements and experiments are reported in which this agent is compared with the most used of the oleic acid esters, namely, Tween 80. Triton A20 is miscible in all proportions with water and can be handled like Tween 80 in the preparation of liquid and agar media. By adding various amounts of Tween 80 or Triton A20 to a basal medium containing amino acids, buffer salts and crystalline bovine serum albumin, the effect of these wetting agents on the growth of virulent and avirulent tubercle bacilli could be readily studied. Also the influence of blood serum on the growth-dispersing effect of these agents was observed and finally their combination with either oleic acid, sphingomyelin or crystalline serum albumin was investigated. The following results were noted. Tween 80 loses its ability to disperse cultures of tubercle bacilli in media containing serum, Triton A20 does not. Tween 80 increases the yield of growth, probably by supplying oleic acid to the bacilli, Triton A20 does not. In concentrations sufficient to cause dispersed growth, Tween 80 (purified by removal of unesterified fatty acid) and Triton A20 are completely innocuous to virulent tubercle bacilli. Triton A20, however, exhibits a marked toxic effect on the avirulent variants of mammalian strains. The two wetting agents also differ in their effects on the morphological aspects of the bacterial cultures. Although Triton A20 prevents the formation of large amorphous bacillary clumps, it is less effective than Tween 80 in preventing the formation of long bacillary strands. With Tween 80 these cords of bacilli are not formed, resulting in a better dispersion of the bacilli.—*The effect of wetting agents on the growth of tubercle bacilli*, R. J. Dubos & G. Middlebrook, *J. Exper. Med.*, July 1, 1948, 88: 81 —(J. S. Woolley)

**Tuberculous Droplet Infection in Rabbits II**—The fate of tubercle bacilli inhaled after tuberculosis already had been established by droplet infection has been studied to determine the effects of developing resistance in infected animals. At intervals of two to eleven weeks after normal rabbits had inhaled small numbers of virulent bovine tubercle bacilli in droplet nuclei, groups of these animals received another single exposure during which each animal inhaled about 20,000 separated bacilli. Normal control rabbits receiving this dose died within four weeks. Rabbits reinfected within four weeks of the initial exposure seemed to be about as susceptible to further implantation of separated organisms as were normal animals. However, reinfection tubercles always contained far smaller numbers of bacilli than initial tubercles of the same age. This difference was present even in animals re-exposed at two weeks. When reinfection was delayed five weeks, however, the bacilli of reinfection did not grow sufficiently in most animals to induce new tubercles in the lungs. It is suggested that after five weeks many rabbits become immune to reinfection although, in a few, exposure to massive reinfection seemed to stimulate the progress of the initial infection. It is possible that such reinfection so saturated the defense mechanism of some animals that, although the bacilli of reinfection were destroyed, those in the initial focus increased more rapidly than would be expected. It is also possible that a sensitization reaction may have been present. The basic effect of the acquired resistance of rabbits to tubercle bacilli in these experiments seems to be an inhibition of the multiplication of the bacilli. *Tuberculosis of rabbits induced by droplet nuclei infection. II. Response to reinfection*, H. L. Ratchliffe & W. F. Wells, *J. Exper. Med.*, June, 1948, 87: 585 —(J. S. Woolley)

**Tuberculoproteins II**—Preparations obtained from unheated culture filtrates of tubercle bacilli were sufficiently distinctive according to their sedimentation and diffusion diagrams to warrant an investigation of their

serological identities Only two serologically different proteins were found in these unheated filtrates One of them was the protein which had a sedimentation constant of 3.4 S and the other was in filtrate fractions with a constant of 2 S The material giving the higher rate was practically homogeneous antigenically and was in a fraction precipitated by one-quarter saturated ammonium sulphate at pH 4.4 The fractions obtained by full saturation contained only the second antigenic entity, fractions obtained by one-half and three-quarters saturation appeared to be mixtures of the two That these proteins were distinct was demonstrated by three methods quantitative precipitin and precipitin absorption tests with rabbit antisera, skin tests in guinea pigs actively sensitized with the culture filtrate fractions, and skin tests in passively sensitized guinea pigs In the guinea pigs sensitized with the first of the two proteins the sensitization was against only the homologous fraction All fractions proved active for tuberculin-sensitive human beings or tuberculous guinea pigs A third antigen of unknown nature was found by means of the precipitin test but only in certain fractions from the virulent culture filtrate The protein with the constant 3.4 S could not be demonstrated serologically in an Old Tuberculin made from the same culture filtrate as the unheated preparation from the virulent organism — *The proteins in unheated culture filtrates of human tubercle bacilli II Determination of serological properties*, J R McCarter & E B Bevilacqua, *J Exper Med*, March, 1948, 87 245 — (J S Woolley)

**Complement Fixation in Psittacosis** — The serum complement fixation reaction, supplemented by clinical and epidemiologic data, furnished the basis for a diagnosis of psittacosis in 21 cases, in none of which was the disease fatal A fourfold or greater rise in antibody titer during the course of the illness occurred in the serum of 9 persons, from one of whom psittacosis virus was isolated Serum from 12 persons had a significant titer (1 to 32) when it was first secured ten days or later after

the onset of the disease All the patients had manifested the clinical characteristics of the disease However, pulmonary lesions were not demonstrated by roentgenograms of the chest in 4 of 16 persons examined All the patients reported intimate contact with birds, chiefly pet parakeets and pigeons The serum complement fixation reaction became positive about the seventh to the tenth day of the disease, achieved a maximum titer about the fifteenth to the thirtieth day and persisted, though in low titer, as long as the serum was tested — *Complement fixation reactions in psittacosis*, D J Davis, *Arch Int Med*, May, 1948, 81 623 — (G C Leiner)

**Humidity and Air-borne Bacteria** — An understanding of the influence of atmospheric conditions on the viability of air-borne microorganisms is essential to any attempt to formulate the epidemiology of air-borne infections In the present study bacterial suspensions were atomized into an experimental chamber under controlled conditions of temperature and relative humidity The most striking fact revealed by these tests was the demonstration of the existence of a narrow range of relative humidity, in the vicinity of 50 per cent, which is rapidly lethal for microorganisms freshly sprayed into the atmosphere from a broth suspension The ultimate extent of dehydration depends on the relative humidity, since the droplet eventually comes into a condition of equilibrium with the atmosphere The viability of pneumococcus, Type I, sprayed into the atmosphere from a liquid suspension was measured as a function of the relative humidity When broth, saliva, or 0.5 per cent saline solution was employed as the suspending medium, a very high mortality rate was observed at relative humidities in the vicinity of 50 per cent However, at humidities above or below this value the microorganisms survived for long periods Measurement of the rate of settling of droplets employed in these experiments demonstrated that the disappearance of microorganisms from the air is a true lethal process rather than a manifestation of aerosol collision processes

When a saline-free fluid was used however, the sharp peak in death rate at intermediate relative humidities disappeared. The lethal effect of intermediate relative humidities on pneumococci atomized from a saline-containing suspension was increased when the particle size of the atomized droplets was increased or when the temperature was raised. Cultures of group C hemolytic streptococcus and staphylococcus sprayed from a broth medium exhibited the same general survival pattern as a function of relative humidity although the mortality rates were smaller than that of the pneumococcus. These effects can be explained by assuming the existence of a critical degree of cellular dehydration at which microorganisms become much more sensitive to toxic agents than in states where either more or less water is bound to the cell.—*The lethal effect of relative humidities on air-borne bacteria*, E W Dunklin & T T Puck, *J Exper Med*, February 1, 1948, 87 87—(J S Woolley)

**Humidity and Influenza Virus**—To study the effect of air moisture on the infectivity of influenza virus, white mice were exposed to atmospheres containing known amounts of atomized influenza A virus (PR8 strain) of constant potency under conditions of varying humidity. It was found that an amount of atomized virus suspension which produced a 100 per cent mortality rate in animals exposed at 30 and 80 per cent relative humidity, respectively, resulted in the death of only 22.5 per cent of mice at a humidity of 50 per cent. The humidities between these values gave intermediate results. The infectivity of the air-borne virus decreased so rapidly at a humidity of 50 per cent that it was impossible to secure a 100 per cent mortality rate in the exposed mice even by greatly increasing the dose of virus atomized. The use of a dialyzed virus suspension at a humidity of 50 per cent resulted in the death of all exposed mice. This suggested that the deleterious influence of humidity was related to the presence of sodium chloride in the atomized suspension. These findings with influenza virus closely

resembled those obtained by Dunklin and Puck with pneumococci, streptococci, and staphylococci which would suggest that the factor responsible for the lethal effect of humidity is common to moist particles containing either the above mentioned bacteria or influenza A virus.—*The influence of relative humidity on the infectivity of air-borne influenza A virus (PR8 strain)*, W Lester, Jr, *J Exper Med*, September 1, 1948, 88 361—(J S Woolley)

**Pulmonary Edema due to Epinephrine**—The intravenous injection of epinephrine increases the central action of neurotropic substances at least fivefold and in the course of such injections many rabbits develop severe dyspnea. This is followed by pulmonary edema with pink foam and fluid pouring from the nostrils and mouth, convulsive struggling and death. Pulmonary edema can be produced regularly by injecting 5 cc of water or physiological saline solution with the epinephrine, without the additional fluid, pulmonary edema occurs only sporadically. Combining the epinephrine with depressants like alcohol or paraldehyde prevents the development of pulmonary edema. Angiocardiography was used to study the pathogenesis of this epinephrine pulmonary edema by injecting first epinephrine and then thorastin into the ear vein of rabbits. Radiographs taken immediately after the injections revealed the jugular veins filled to capacity with the opaque material. The dilated veins could be followed to the right auricle and 40 seconds after the injection no opaque dye was visible in the left heart or aorta. Because of the increased pressure in the pulmonary circulation and the right heart, the injected dye took the route of least resistance and spread backwards into the peripheral tributaries of the jugular veins in the head. No trace of the opaque dye could be seen in the radiographs of the control rabbits. Experimental observations indicate that a sensitized heart may respond abnormally to small amounts of epinephrine. Although large doses are required to produce left ventricular failure and pulmonary edema in normal ani-



mals, small amounts of epinephrine or similar pressor substances may significantly affect a seriously weakened left ventricle in man — *Angiocardiographic experiments on the pathogenesis of adrenalin pulmonary edema in rabbits*, A Elkeles, *Brit J Radiol*, September, 1948, 21 472 — (L Hyde)

**Blood Pressure and Respiration**—By means of the cardiac catheterization technique and a Hamilton manometer, pressure tracings were obtained from the right auricle and ventricle of 4 normal subjects, of 6 patients with chronic pulmonary disease, and of 4 patients with auricular fibrillation and heart failure. A study was made of the influence of respiration on the intracardiac pressures. In normal subjects the average maximum pressure in the auricle was 22.5 mm of water during expiration and 7.5 mm of water during inspiration, the average minimum pressure was 6.0 mm of water during expiration and minus 10 mm of water during inspiration. The average systolic blood pressure in the right ventricle was 27.25 mm of mercury during expiration and 22.25 mm of mercury during inspiration, the average diastolic pressure was 5.75 mm of mercury during expiration and minus 0.5 mm of mercury during inspiration. In patients with chronic pulmonary disease in the absence of heart failure, only the right ventricular systolic pressure was elevated. Systolic pressure in the right auricle and diastolic pressure in the right ventricle were normal. In patients with chronic pulmonary disease in the presence of heart failure, both systolic and diastolic right ventricular pressures were elevated. Auricular pressures were also elevated because of the hindrance of auricular emptying which resulted from the increased diastolic ventricular pressure. In normal subjects and in patients with chronic pulmonary disease, with or without heart failure, intra-auricular and intraventricular pressures were lower during inspiration and higher during expiration. The respiratory variations of intra-auricular pressure are ascribed to (1) variations in the intrapleural pressure and (2) action of the

elastic fibers of the lungs which, during inspiration, distend the auricular walls. The respiratory variations of intraventricular pressure are ascribed to (1) variations in the intrapleural pressure and (2) decreased peripheral resistance in the pulmonary circuit during inspiration. In patients with heart failure and auricular fibrillation, maximum and minimum pressures in the right auricle and right ventricle were abnormally elevated and did not change during respiration. The lack of respiratory variation in the pressures in the right auricle and in the right ventricle is ascribed to repletion and distention of the right auricle and to pulmonary stasis, respectively. (Authors' Summary)—*Intracardiac blood pressure in human subjects and its relation to the respiratory phases*, A Battro, H Bidoggia, E Pietrafesa & F E Labourt, *Am Heart J*, January, 1949, 37 11 — (G C Lerner)

**Artificial Respiration**—Artificial respiration was produced in the cat, dog, monkey and rabbit by electrical stimulation of one or both phrenic nerves. Adequate minute volumes of respiration, arterial blood oxygenation and elimination of carbon dioxide were achieved in the absence of spontaneous respiration by submaximal stimulation of one phrenic nerve. A severalfold increase in ventilation was seen with bilateral phrenic nerve stimulation. Tidal volume, minute volume and, therefore, arterial oxygen and carbon dioxide tensions, can be regulated by adjustment of the peak voltage used for the stimulation. Artificial respiration was maintained as long as twenty-two hours — *Electrophrenic respiration*, S J Sarnoff, Esther Hardenbergh & J L Whittenberger, *Am J Physiol*, October 2, 1948, 155 1 — (G C Lerner)

**Pulmonary Capillary Pressure**—A venous catheter was introduced into the pulmonary artery of dogs and wedged into a distal ramification so as to obstruct its lumen. Pressures beyond the point of obstruction were recorded through a hole in the tip of the catheter with a Hamilton manometer and with

a saline column. An arterial catheter was introduced by way of the carotid artery and left side of the heart into a pulmonary vein in similar fashion and pressures were similarly recorded. In dogs, the pressures recorded with a Hamilton manometer through the catheter blocking the pulmonary artery varied between 5 and 8 with an average of 6 mm of mercury while those measured simultaneously through the catheter blocking the pulmonary vein varied between 6 and 14 with an average of 10 mm of mercury. The former is probably lower than true pulmonary capillary pressure by the "velocity factor" and the latter too high by the same factor. It is suggested that the true mean capillary pressure with unobstructed flow normally lies between these two figures, the average in 6 animals varying from 5.5 to 10 mm of mercury with an average of 8.3 mm of mercury. It is considered that damage to the left side of the heart from arterial catheterization prohibits its use in man (Authors' Summary)—*Pulmonary capillary pressure in animals estimated by venous and arterial catheterization*, H K Hellems, Florence W Haynes, L Dexter & Th D Kinney, *Am J Physiol*, October, 1948, 55: 99—(G C Leiner)

**Joint Reflexes and Respiration**—Passive flexion of the hind limbs of cats and dogs is accompanied by variable changes in rate and depth of respiration. These changes do not appear to result from the stimulation of receptors in the knee joint. Other types of stimuli, including those secondarily induced by the flexion, such as movements of the trunk, were as effective in stimulating respiration. Similar changes occurred in dogs whose knee joints had been partially denervated. Electric stimulation of nerves to the knee joint was effective only at intensities great enough to activate slower conducting fibers, resulting in what appeared to be pain hyperpnea. It is concluded that, under the conditions of anesthesia used, joint reflexes do not play a significant role in the production of the respiratory changes during passive flexion. It is also concluded that there is no satisfactory evidence

which indicates that limb reflexes are important in the regulation of respiration during exercise in man (Authors' summary)—*Joint reflexes and regulation of respiration during exercise*, E Gardner & J Jacobs, *Am J Physiol*, June, 1948, 153: 567—(G C Leiner)

#### PUBLIC HEALTH AND EPIDEMIOLOGY

**Prevention of Tuberculosis**—Dr Wyndham E B Lloyd, tuberculosis officer for South Devon, has emphasized recently that tuberculosis is not only a disease but a social and economic problem. To prevent infection the first step is to discover the individuals who harbor the disease. When the patients have been found, they must be treated and educated so that they are no longer a danger to others. This is especially true since the main reservoir of infection is the person whose sputum contains tubercle bacilli but who does not know or care, one of the most common is the middle-aged person who has been diagnosed as having "bronchitis." To prevent the spread of tuberculosis through milk, all dairy herds should be tuberculin-tested and, if the herds are untested, milk should be heat-treated. Since the establishment of the National Health Insurance Service in 1911, patients in the British Isles are sent by their own doctors to tuberculosis officers. Contacts then are called in for examination. Mass miniature roentgenography is now also available. Too much stress cannot be laid on environment in the prevention of tuberculosis. The important factors include adequate housing, water supply, proper ventilation, and absence of overcrowding. Children must have sufficient diet and "there must be freedom from want, from fear, and from insecurity." Nothing is gained by sending a patient from a sanatorium back to overcrowded slum conditions. At first sight, the results of the work done in combating tuberculosis seem very unsatisfactory. Infections seem to be increasing, the total number of cases of the disease is greater, the waiting lists for sanatoriums are long. However, notifications are no indication of the increase of the disease, for the more the search,

the greater the number of cases that will be found Between 1914 and 1943 the crude death rate for pulmonary tuberculosis has been reduced by 50% What is most needed, Doctor Lloyd concluded, is an enlightened public—*Prevention of tuberculosis Environmental factors (Editorial), Brit M J, November 18, 1948, 4584-870*—(R W Clarke)

**Photofluorography**—Experience in Zurich, Switzerland, shows that a case finding program by means of photofluorography is not only financially possible but profitable Of 16,585 adults examined, 74 per cent were normal, 19.9 per cent had unimportant abnormalities and 6.1 per cent were judged to be in need of further investigation Of these, 1.56 per cent needed either supervision or treatment for

tuberculosis, 0.76 of the 1.56 per cent were previously unrecognized Previously unrecognized infectious tuberculosis was present in 0.16 per cent The authors calculate that the initial cost of the program and the operative expenses over two years (1945 and 1946) have already been saved the public if one assumes that each of the 24 infectious individuals discovered would be responsible for 3 or 4 new cases if allowed to go undetected This program should prove even more profitable as the initial cost of the equipment is distributed over more than a two year period—*Abklärungsergebnisse und Wirtschaftlichkeit des Schirmbildverfahrens in der Stadt Zürich, H O Pfister & W Schwarz, Schweiz med Wchnschr, January 31, 1948, 78-87*—(H Marcus)

# SIMPLE TESTS OF VENTILATORY FUNCTION FOR USE IN THE SANATORIUM OR CLINIC<sup>1 2</sup>

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## INTRODUCTION

About seven years ago a series of talks and articles on bronchspirometry (1, 2, 3, 4) aroused widespread interest in this country in the subject of pulmonary function. After an initial wave of enthusiasm, many chest physicians and thoracic surgeons abandoned thoughts of utilizing functional tests because they thought that the necessary apparatus was too complicated and expensive, detailed knowledge of pulmonary physiology was needed to execute and understand the procedures, and the performance of the tests would be too consuming of their time. Consequently, at the present time detailed respiratory studies are being carried on in a very few centers, but none are being done in a majority of institutions or by most practitioners. It is not generally appreciated that there are some simple, practical tests of pulmonary function which can give much needed information concerning many patients with lowered breathing reserve. These tests can be performed by any clinician or surgeon without expert knowledge of pulmonary physiology, and require the use of uncomplicated, inexpensive apparatus for only a few hours each month.

With suggestions and encouragement from Dr. George Wright of Trudeau, New York, a program of simple, practical tests of ventilation was initiated at Laurel Heights in 1942. In the past six years, 1,150 studies have been performed on 410 patients. It is obvious that simple tests of ventilation alone are inadequate if the objective is exhaustive study of pulmonary physiology. Nevertheless these simple tests have been of great practical value in the management of patients. They have served to detect the presence or imminence of dyspnea and to predict and follow the effect of collapse therapy with a degree of accuracy which is generally quite adequate for clinical purposes. To say the least, such tests have led to conclusions regarding function which have proved far more reliable than those derived from "clinical judgment" and study of chest roentgenograms.

The purpose of this paper is to describe the apparatus and the method used in performing these ventilatory tests, to show illustrations of their application, and to review the end results of function in a group of cases after operation.

The apparatus (figure 1) consists of a 100 liter Douglas Bag, a high velocity one-way valve, connecting hose and couplings, a noseclip, a converted gas meter, and a stopwatch. This entire equipment can be purchased for about two hundred dollars.

<sup>1</sup> From the Laurel Heights State Tuberculosis Sanatorium, Shelton, Connecticut.

<sup>2</sup> Presented before the Fall Meeting of the Eastern Section of the American Trudeau Society at the Rutland State Sanatorium, Rutland, Massachusetts, on October 15, 1948.

## METHOD

Four parts comprise this method of evaluation of a patient's ventilatory function

- (a) the walking ventilation,
- (b) the maximum breathing capacity,
- (c) the ratio  $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$  and its relationship to dyspnea, and
- (d) careful fluoroscopy of the chest

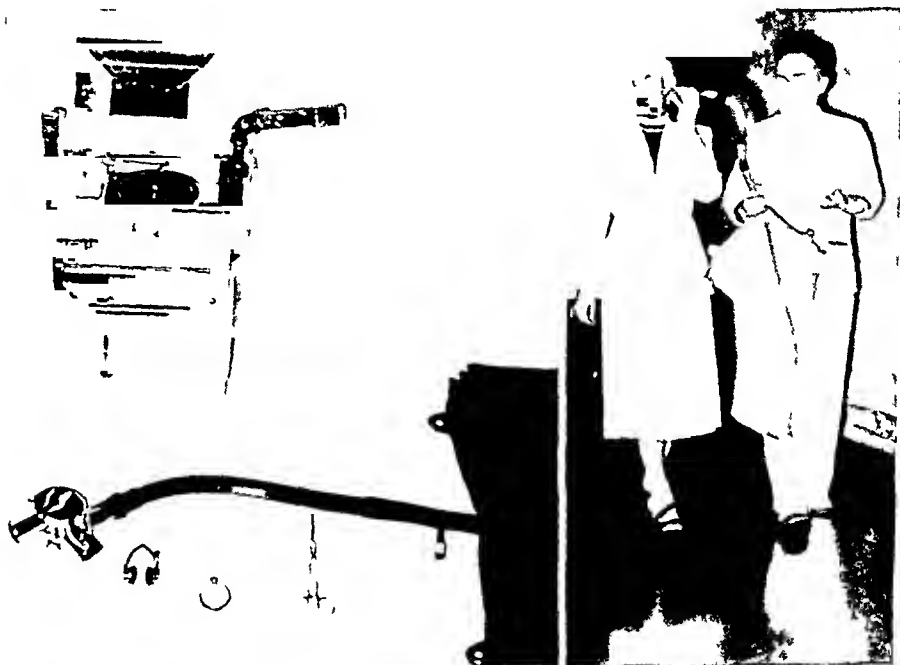


FIG 1 (Left) The apparatus: a 100 liter Douglas Bag, high velocity one way valve, connecting hose and couplings, noseclip, converted gas meter and stopwatch

FIG 2 (Right) Performing the walking ventilation test

### *The Walking Ventilation (WV)*

The walking ventilation test is performed by having the patient walk slowly on a level surface, breathing as easily and naturally as possible through the one-way valve into the Douglas Bag. The pace is 180 feet per minute. The test is started by applying the noseclip to the patient. Then the patient merely walks for one minute beside the operator, who, during this initial period, carries both the Douglas Bag and the valve. This one minute "warm-up period" is to familiarize the patient with the pace and to bring his rate and depth of breathing to the walking level. Having done this, the patient and the operator continue to walk at the same pace, the patient is instructed to place the mouthpiece of the valve into his mouth, and the operator resets his stopwatch. As he walks for

the next three minutes, the patient breathes in a natural manner through the valve into the Douglas Bag, which is carried by the operator (figure 2). Exactly at the end of three minutes the valve is taken from the patient's mouth, the connecting hose to the bag is promptly clamped off, and the noseclip is removed. The patient is immediately questioned about the presence and degree of dyspnea. The air in the Douglas Bag is measured by running it through a gas meter calibrated in liters. The resulting figure, divided by three, gives the walking ventilation in liters per minute.

Values for the walking ventilation test vary from 7 to 30 liters per minute in different patients. Most patients have a walking ventilation in the range of 12 to 19 liters per minute. *Of importance is the fact that in the great majority of patients the walking ventilation remains remarkably constant.* For example, a patient with a walking ventilation of 14 liters per minute can be expected to have a walking ventilation at or near 14 liters per minute before and after spread of disease, before and after clearing of disease, and before and after collapse therapy.

Some other details of the walking ventilation test should be mentioned. While the test is being performed, a check on the distance covered at 15 second intervals aids in maintaining an even pace. The patient is repeatedly instructed to "breathe easily, just as you do when you walk on the ward." Occasionally an apprehensive patient will give an initial artificially high value for his walking ventilation. If this is suspected, or if the patient has a walking ventilation of 20 liters or more on the first test, it should be repeated a second or third time the same day or later to determine the true level.

Degree of dyspnea at the conclusion of the walking test is recorded as  
none

slight (aware of labored breathing, but not uncomfortable)

moderate (uncomfortable, but could continue walking), or

severe (could not continue walking or did not complete the test)

Dyspnea of the throat should not be confused with slight dyspnea.

### *The Maximum Breathing Capacity (MBC)*

The maximum breathing capacity is determined by having the patient breathe as hard and as fast as he can for exactly 30 seconds through the high velocity one-way valve into the Douglas Bag (figure 3). The air in the bag is measured by passing it through the gas meter. The resulting value, multiplied by two, gives the maximum breathing capacity in liters per minute. A healthy male has a maximum breathing capacity of about 150 liters per minute and a healthy female, a maximum breathing capacity of about 100 liters per minute. Any disease or condition which impairs the function of the pulmonary parenchyma, the pleurae, the ribs, the diaphragm, the bronchi, or any combination of these five anatomical components of the chest, proportionately reduces the maximum breathing capacity.

Careful effort is made to get the patient to put forth his best effort when doing the maximum breathing capacity. Most patients perform best in a sitting position, in a chair or with their legs hanging over the side of the bed. It is worth-

while to have a new patient watch an experienced one do both the walking ventilation test and the maximum breathing capacity before attempting it himself. Some patients, in a spirit of competition, exert themselves more before in audience of one or two other patients who are waiting their turn. Care must be taken that the nose clip is snug and that the patient does not remove his lips from the mouthpiece. The importance of the test to the patient is emphasized and reassurance should be given that the test will not result in spread of disease or hemoptysis. The patient is instructed to "breathe as hard and fast as you can for one-half minute." Two steady, deep breaths a second is a good rate. Rates of breathing that are too slow or too rapid are inefficient. It frequently is desirable to mark time with the patient's breathing and to hold the stop watch before



FIG. 3 Determining the maximum breathing capacity

him. The patient should be encouraged to his very best effort during the entire 30 second period. Unless both the operator and the patient are satisfied that the exertion has been maximum, the test is repeated on the same day or later. By observing these precautions, the maximum breathing capacity can be reproduced within 5 per cent.

*Relationship of the Ratio  $\frac{\text{Walking Ventilation}}{\text{Maximum Breathing Capacity}}$  to Dyspnea*

There is a definite relationship between the ratio  $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$  and the presence and degree of dyspnea (5)

When  $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$  is below .35, dyspnea is not present

When  $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$  approximates .35 slight dyspnea is present

When  $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$  approximates 45, moderate dyspnea is present

When  $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$  exceeds 50, severe dyspnea is present at the end of the walking test

Two important facts must be kept in mind first, *the walking ventilation remains constant in the individual patient*, and, second, *dyspnea upon walking becomes severe as the ratio  $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$  exceeds 50*. Thus, it becomes apparent that disease or collapse therapy that causes *reduction of a patient's maximum breathing capacity to a level lower than twice his walking ventilation results in severe dyspnea when the patient is walking*.

The following is a hypothetical example of the development of dyspnea with progressive lowering of the maximum breathing capacity in a patient whose walking ventilation is 16 liters per minute

<i>MBC</i>	<i>W V</i>	<i>RATIO <math>\frac{W V}{MBC}</math></i>	<i>DYSPNIA</i>
64 L	16 L	25	none
46 L	16 L	35	slight
36 L	16 L	45	moderate
30 L	16 L	53	severe

### *Fluoroscopy of the Chest*

Once the determinations have been made of the breathing requirement for walking, the maximum breathing capacity, and the ratio between the two, the patient is carefully fluoroscoped. The operator's eyes should be well accommodated to darkness before beginning the examination. The chest is viewed upon quiet breathing and also while efforts are made of both slow and rapid maximum inspiration and expiration. The following details are observed: movements of the ribs and diaphragms, shift of the heart or mediastinum, evidence of trapping of air in a lobe or lung, and, in the patient with pneumothorax, the degree of collapse and motion of the collapsed lung, and the presence of fluid.

Rib motion and diaphragm motion of each hemithorax is recorded separately in percentages of normal as estimated by the operator. With practice this can be done with reasonable accuracy. By adding the percentages of rib motion and diaphragm motion on each side, it is possible to arrive at an estimate of the ratio of the ventilation carried on by each lung separately. Thus a patient estimated to have 100 per cent normal rib motion and 100 per cent normal diaphragm motion on the right side of the chest and 25 per cent normal rib motion and 25 per cent normal diaphragm motion on the left side of the chest has a ratio of 200 (right) to 50 (left). Expressed in another way this means that the right lung is estimated to be doing 80 per cent of the total ventilation.





FIG 4 (Upper left) Normal chest, deep inspiration

FIG 5 (Upper right) Normal chest, deep expiration. There is equal "clouding" of the two lungs

FIG 6 (Center left) Marked stenosis of the left main bronchus, deep inspiration

FIG 7 (Center right) Marked stenosis of the left main bronchus, deep expiration. There is "trapping" of air in the left lung and the heart and mediastinum are pushed to the right side

FIG 8 (Lower left) Bilateral emphysema in a patient with silico-tuberculosis, deep inspiration

FIG 9 (Lower right) Bilateral emphysema. When rapid expiration is attempted the hemidiaphragms rise only part way in two seconds (A). Continued expiratory effort results in slow, progressive elevation to the maximum level (B) at the end of ten seconds

Uniform aeration is noted throughout the lung parenchyma when the density of the normal lung at deep inspiration is observed by fluoroscopy (figure 1). When this is followed by a rapid, deep expiration, emptying of the air from the parenchyma promptly produces a homogeneous haze, more dense over the lower two-thirds of the lung (figure 5). When, on attempted rapid expiration, air is retained in a lobe or lung by emphysema or by marked bronchial stenosis, the area affected fails to cloud and this phenomenon is referred to as "trapping." When trapping is a result of bronchial stenosis, the heart and mediastinum shift toward the side of the stenosis on deep inspiration and are pushed toward the contralateral side on deep expiration (figures 6, 7). If emphysema is present, the diaphragm (or diaphragms, if the condition is bilateral) may move but little at the very beginning of attempted rapid expiration and then slowly rise as the inelastic, emphysematous lung parenchyma expels the air in a period of five or more seconds (figures 8-9). In the absence of stenosis or emphysema, deep expiration can be completed in one to two seconds.

It is important to take into consideration trapping caused by stenosis when attempting to estimate the ventilation carried on by each lung separately. If rapid breathing is being carried out, as when the maximum breathing capacity is being determined, very little air has a chance to get in and out of the lobe or lung whose bronchus is markedly stenotic. In this situation practically all of the total ventilation is performed by the other lobes the bronchi of which are patent. For example, before resection the patient with the marked stenosis of the left main bronchus (figures 6, 7) had a maximum breathing capacity of 58 liters per minute. It was estimated that nearly all of this total ventilation was being performed by the right lung and that only a small amount of air was being ventilated by the left lung distal to the stenotic bronchus. That this assumption was correct is supported by the finding of a maximum breathing capacity of 55 liters per minute after the left lung was removed at operation.

When trapping is a consequence of emphysema it must be remembered, when contemplating collapse or resection, that an emphysematous lung is a poorly functioning lung. It is often unwise, therefore, to perform thoracoplasty or resection on one lung if the contralateral lung shows signs of marked emphysema. On the other hand, performing such an operation on the emphysematous lung is possible and even may be desirable functionally if the contralateral lung is not emphysematous and demonstrates evidence of sufficient ventilatory reserve.

Conditions other than stenosis of the bronchus can produce mobility of the mediastinum. Movement of the mediastinum to a diseased side on inspiration may denote the presence of fibrosis reducing the elasticity of the parenchyma of that lung. With pneumothorax a mobile heart and mediastinum may shift to the contralateral side on expiration.

If lobes collapsed by pneumothorax expand and contract well with inspiration, it is an indication that ventilatory function is well preserved in those lobes.

Thus it may be seen that much information relative to the total ventilation and to the individual ventilation of the two lungs can be gained, with experience, from careful fluoroscopy.

## APPLICATION OF VENTILATORY TESTS

*Thoracoplasty*

Since thoracoplasty is an irreversible procedure, it is essential to determine in advance whether or not the patient has enough breathing reserve to tolerate this operation. As a corollary to this, the surgeon wishes to know how many ribs he can remove, if necessary, or to how few ribs he must limit his collapse. *The walking ventilation remains constant before and after thoracoplasty and severe dyspnea occurs on walking when the ratio  $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$  exceeds 50.*

*It follows then that the maximum breathing capacity in any individual patient must not be reduced by operation to a level below twice the patient's walking ventilation if severe dyspnea on walking is to be avoided.* Moreover, in our experience, in order to avoid dyspnea, it is necessary that the patient be left after operation with a maximum breathing capacity of not less than 30 liters per minute, no matter how low his walking ventilation may be.

When the maximum breathing capacity before operation is high, the reserve is ample and no concern is felt about thoracoplasty even though the thoracoplasty side is contributing a fair amount of the total ventilatory function and the operation must be an extensive one.

*Example (Case 1)* The patient was a 33 year old male with a four centimeter cavity in the apex of the left lung (figure 10). His maximum breathing capacity was 136 liters before operation. Walking ventilation was 18 liters. As twice 18 is 36 liters, the maximum breathing capacity of this patient, if necessary, can be reduced by operation to 36 liters although it is never wise to squander function. Rib motion and diaphragm motion on the right side were both estimated to be 100 per cent of normal. The left diaphragm moved 100 per cent of normal, while the rib motion on the left was slightly reduced (75 per cent of normal). From this it is seen that the right or "good" side was contributing slightly more than half of the total maximum breathing capacity of 136 liters. The surgeon was able to remove 8 ribs on the left side without fear of producing eventual dyspnea. After operation the maximum breathing capacity was 82 liters (figure 11). Walking ventilation remained relatively constant at 19 liters. Ratio of  $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$  postoperatively was .23. With the ratio less than .35, the patient had no dyspnea when walking.

Likewise, it is feasible to perform thoracoplasty when the preoperative maximum breathing capacity is only moderately high, or even lower, if the operation is to be done on a poorly functioning side.

*Example (Case 2)* The patient was a 40 year old woman who had active parenchymal disease and an empyema pocket on the right which required a 7-rib thoracoplasty with removal of the anterior rib sections (figure 12). Her walking ventilation was 18 liters. In this instance, as in Case 1, the maximum breathing capacity could, if necessary, be reduced to 36 liters, or twice her walking ventilation. Her maximum breathing capacity before operation was 75 liters, so that she did not have the ample reserve of the man with the maximum breathing capacity of 136 liters. On the other hand, fluoroscopy revealed that the ribs and diaphragm each moved only 25 per cent of normal on the right side as compared to 100 per cent normal motion of the left ribs and 100 per cent normal motion of the left diaphragm. Adding the percentages of rib and diaphragm motion on each side gave a ratio of 50 to 200,

or 1 to 4, in favor of the left side. Hence the left side was estimated to contribute four-fifths, i.e., 60 liters of the total maximum breathing capacity of 75 liters. This was borne out by the



FIG 10 (Case 1) (Upper left) Before left thoracoplasty. Rib motion, right, 100 per cent, left, 75 per cent. Diaphragm motion, right, 100 per cent, left, 100 per cent. M B C, 136 liters, W V, 18 liters, ratio, 13.

FIG 11 (Case 1) (Upper right) After left thoracoplasty. M B C, 82 liters, W V, 19 liters, ratio, 23.

FIG 12 (Case 2) (Lower left) Before right thoracoplasty. Rib motion, right, 25 per cent, left, 100 per cent. Diaphragm motion, right, 25 per cent, left, 100 per cent. M B C, 75 liters, W V, 18 liters, ratio, 24.

FIG 13 (Case 2) (Lower right) After right thoracoplasty. M B C, 60 liters, W V, 19 liters, ratio, 31.

results of tests after extensive right thoracoplasty (figure 13). Elimination of the ventilation of the right lung gave a postoperative maximum breathing capacity of 60 liters. Walk-

ing ventilation remained constant at 19 liters. Ratio of  $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$  after operation was .31 and the patient was not dyspneic.

A patient with moderate or low maximum breathing capacity before operation may even tolerate thoracoplasty on the side of *better* function, provided the operation is sharply restricted in extent so as to produce a highly selective type of pulmonary collapse affecting only the diseased portion of the lung.

*Example (Case 3)* This 36 year old woman had previously received left pneumothorax, with subsequent expansion of the left lung. Fluoroscopy revealed 75 per cent normal rib motion and 75 per cent normal diaphragm motion on the right side and only 25 per cent



FIG 14 (Case 3) (Left) Before right thoracoplasty. Rib motion, right, 75 per cent, left, 25 per cent. Diaphragm motion, right, 75 per cent, left, 25 per cent. M B C, 40 liters, W V, 11 liters, ratio, .28.

FIG 15 (Case 3) (Right) After selective right thoracoplasty. M B C, 37 liters, W V, 13 liters, ratio, .35.

normal rib motion and 25 per cent normal diaphragm motion on the left side (figure 14).

Adding the percentages of rib and diaphragm motions on each side gave a ratio of 150 to 50, or 3 to 1, in favor of the right side. She needed a thoracoplasty on the *right* for a small cavity which was fortunately situated in the extreme apex. Also in her favor was a low preoperative walking ventilation of 11 liters per minute. Her maximum breathing capacity of 40 liters per minute before operation could be reduced to our minimum standard of 30 liters. The surgeon did an excellent selective 5 rib right thoracoplasty, with partial right scapulectomy. He was careful to leave the anterior rib sections below the level of the fifth vertebral spine in order to preserve as much of the function of the lower two thirds of the right lung as possible (figure 15). Maximum breathing capacity following operation (37 liters) was only slightly less than the preoperative value. Walking ventilation changed only to 13 liters. With the resulting ratio of  $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$  at .35, the patient experienced only slight dyspnea when walking on the level.

Wright has shown that the maximum breathing capacity is unchanged or actually improved in 75 per cent of patients following selective apical thoracoplasty.

Thoracoplasty can be performed while pneumothorax is maintained on the contralateral side. Serial tests of ventilatory function in such cases will give information of assistance in (1) maintaining the degree of the pneumothorax at a satisfactory functional level, (2) deciding if thoracoplasty can be performed, and (3) evaluating the end results of function after thoracoplasty and subsequent expansion of the pneumothorax lung.

*Example (Case 1)* The patient was a 39 year old man whose ventilatory function tests yielded the following values:

	MBC	VI	Ratio VI MBC
February 1911—before right pneumothorax	94 L	27 L	29
December 1945—with right pneumothorax	62 L	21 L	31
May 1947—left thoracoplasty performed			
June 1947—after left thoracoplasty, with right pneumothorax	60 L	23 L	38
June 1948—after right lung expanded	74 L	21 L	28

It was essential that this man undergo a left thoracoplasty for emphysema disease. Right pneumothorax was instituted in December 1945, after fresh spread of disease on that side. Before pneumothorax the maximum breathing capacity was 94 liters. With induction and maintenance of right pneumothorax, the maximum breathing capacity was reduced to 62 liters. Seven rib left thoracoplasty was performed in May 1947, while continuing selective right pneumothorax. Maximum breathing capacity was 60 liters in June 1947, after left thoracoplasty and while the right pneumothorax was still being maintained. When the right lung was completely expanded in June 1948, the end result was a maximum breathing capacity of 74 liters. The walking ventilation initially was 27 liters. With the induction of right pneumothorax, it fell to 21 liters and remained stable at that level for the next two and one half years while the thoracoplasty was being done and the right lung was being expanded. The patient was never dyspneic.

Ventilatory tests can demonstrate the imprudence of thoracoplasty for some patients.

*Example (Case 5)* The patient was a 51 year old man with a chest roentgenogram which made it seem probable that he was a suitable candidate for left thoracoplasty. Nevertheless, ventilatory tests showed him to be a very poor risk for operation. Moreover, if thoracoplasty were to be performed, it would have to be complete because of the presence of cavities in the left apex and in the midlung (figure 16). Even though by fluoroscopy the left lung was performing only about one seventh of the total ventilation, this patient had absolutely no reserve. His maximum breathing capacity at 35 liters was already reduced by disease to the level of twice his walking ventilation of 18 liters.

Undoubtedly complete thoracoplasty would further reduce the low maximum breathing capacity and make this patient a pitiful respiratory invalid. It must be remembered also that for a day or two following each thoracoplasty stage the maximum breathing capacity is likely to be reduced to some extent by such factors as the shock of operation, pain, and fluid in the operative site. Even though this is only a temporary slight reduction in the maximum breathing capacity, it may be just enough to precipitate an acute dangerous episode of dyspnea from which a patient without reserve may fail to recover.

It is possible to repeat the maximum breathing capacity after the individual thoracoplasty stages. Seven to thirteen days postoperatively is the best time to

do the test, for by then the patient is relatively comfortable and is able to perform satisfactorily. Thus, in a patient with a low preoperative breathing capacity the test can be repeated between stages and further operations abandoned when it is felt that the maximum breathing capacity is being reduced to an unsafe level. No one stage uniformly depresses the maximum breathing capacity more than any of the others, nor is it possible to say that a given stage will reduce the maximum breathing capacity to the same degree in every patient. These



FIG 16 (Case 5) Rejected for left thoracoplasty. Rib motion: right, 30 per cent, left, 20 per cent. Diaphragm motion: right, 100 per cent, left, 0 per cent. M B C, 35 liters, W V, 18 liters, ratio, .51.

variations are related to the location and extent of the disease under collapse and to the volume of good functioning parenchyma which is being compressed.

*Example* (Case 6) The patient was a 56 year old woman whose ventilatory function tests yielded the following values:

	M B C	W V	Ratio W V M B C
February 1944—before left thoracoplasty	71 L	13 L	.18
May 1944—13 days after first stage	61 L		
June 1944—13 days after second stage	49 L		
July 1944—20 days after third stage	38 L		
March 1945—on one hour outside exercise	47 L	13 L	.28

The patient had a maximum breathing capacity of 71 liters before left thoracoplasty. This fell to 61 liters following the first stage (2 ribs), to 49 liters after the second stage (3 more ribs) and to 38 liters after the third stage (3 more ribs).

It should be observed that this patient's maximum breathing capacity increased 9 liters from the time of the last stage until the patient reached "one hour outside exercise." In our experience, a patient is unlikely to regain ventilatory function of more than 5 to 10 liters during the postoperative period as a result of exercise and improved muscle tone. Frequently the gain is less. There is good circumstantial evidence which suggests that application of tight, encircling binders to the chest for six months after thoracoplasty may cause lasting reduction of maximum breathing capacity in some cases.

### *Resection*

Ventilatory studies are used in selecting patients for resection in much the same manner as for thoracoplasty. We have had opportunity to complete studies on 10 patients who underwent pulmonary resection. From such a small series it is not possible to draw conclusions about the need for thoracoplasty after pneumonectomy. To date our findings support the contention of those investigators who believe that many patients do not require a space-filling thoracoplasty after pneumonectomy, if protecting the function of the remaining lung is the sole objective. Thoracoplasty after resection to prevent undue strain on tuberculosis in the remaining lung is a different matter and frequently there are strong indications for this procedure.

### *Pneumothorax*

Ventilatory studies are of use in pneumothorax patients to determine the ability of the patient to tolerate this type of treatment, to regulate the degree of collapse, and to evaluate the patient's eventual breathing capacity when the lung is expanded. Selective pneumothorax, in collapsing only diseased parenchyma, allows the good lung tissue to continue to function and in this way the maximum breathing capacity need not be reduced at all. If, however, a pneumothorax is sufficiently increased, breathing capacity is lowered in proportion to the degree of collapse of good functioning tissue.

*Example* (Case 7) The patient was a 32 year old woman who had an expanded right lung from a previous pneumothorax (figure 17). On the left she had pneumothorax with 50 per cent collapse and a maximum breathing capacity of 53 liters. A cavity remained open in the left upper lobe. Walking ventilation was 20 liters. These studies revealed that the collapse could be increased, if necessary to close the cavity, until the maximum breathing capacity was reduced to two times 20, or 40 liters. This was tried, but eventually the left pneumothorax was abandoned as ineffective. Fortunately, the cavity closed as the lung expanded. During the expansion of the left lung, fluid formed in this hemithorax. Fifty-two aspirations of pleural fluid were performed before pleural symphysis was obtained (figure 18). It should be noted that the maximum breathing capacity was 104 liters after expansion in spite of the presence of pleural fluid for ten months.

Part of the present trend to condemnation of pneumothorax is based on the assumption that the persistence of pleural fluid during the course of pneumothorax, by thickening of the pleura, frequently causes severe loss of pulmonary function. At Laurel Heights it is rare that severe functional impairment sufficient to produce dyspnea accompanies or follows pneumothorax treatment.



A brief description of our general policy of management of pneumothorax cases should be stated. Pneumothorax which is obviously ineffective at the start because of gross adhesions is abandoned in one or two weeks after induction. Operable adhesions are cut within a few weeks after beginning a pneumothorax. Effective pneumothorax is maintained as "selective" as possible consistent with cavity closure and control of disease and with avoidance of an undue degree of collapse. Tuberculous empyemata and pleural effusions, persisting more than a week or two and extending to or above the dome of the diaphragm, are aspirated assiduously (6). If in the presence of fluid the pneumothorax is to be maintained tentatively, frequent aspiration with an replacement is continued until the pleural space is dry. If, on the other hand, the lung is to be expanded, aspiration

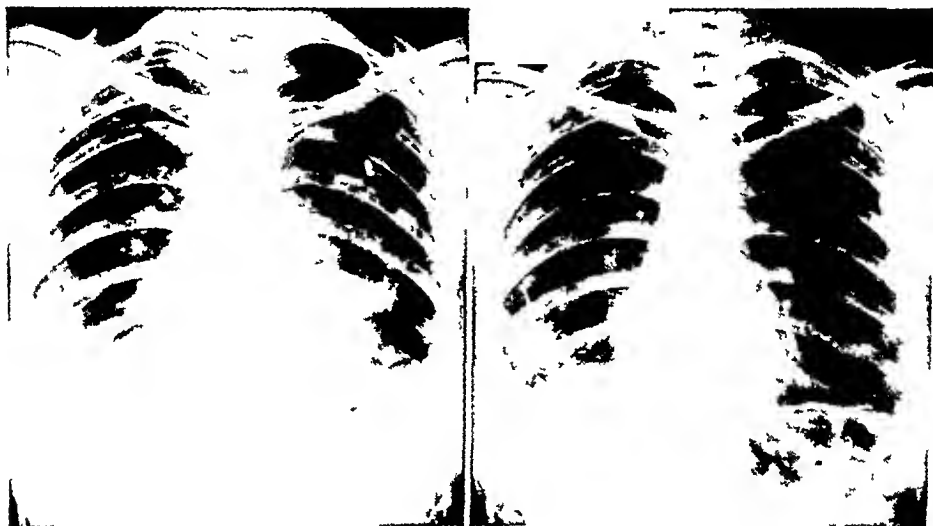


FIG 17 (Case 7) (Left) Expanded right lung with left pneumothorax. M B C, 53 liters, W V, 20 liters, ratio, 38.

FIG 18 (Case 7) (Right) Expanded right lung. After repeated aspiration of fluid from the left chest and expansion of the left lung. M B C, 104 liters, W V, 20 liters, ratio, 17.

without an replacement is continued until pleural symphysis takes place. Effective pneumothorax is maintained for two to three years after the disease is arrested.

Ventilatory studies were performed on 98 cases of pneumothorax before, during, and after expansion of the collapsed lung. All of these patients had moderately advanced or far advanced tuberculosis before pneumothorax was instituted. In 60 of these cases, there was not a sufficient accumulation of fluid to require aspiration. In 38 patients, fluid was repeatedly aspirated during the maintenance of the pneumothorax or as the lung expanded. The fact that pneumothorax treatment, even when complicated by pleural fluid, does not frequently result in severe functional impairment and dyspnea is substantiated by the ratio  $\frac{\text{walking ventilation}}{\text{maximum breathing capacity}}$  in these two groups after expansion of the pneu-

mothorax lung (table 1) A ratio below .35 denotes absence of dyspnea on walking. Less than 10 per cent of each group had dyspnea of any degree on walking after the collapsed lung had been expanded. This is certainly a good functional end result for any form of therapy for moderately advanced and far advanced pulmonary tuberculosis. It is believed that the end results in the cases with fluid would not be as favorable without diligent aspiration. Fluid itself, when properly managed, is not a compelling argument against the use of pneumothorax.

### *Phrenic Paralysis*

The maximum breathing capacity was reduced more than 10 liters in 11 of 16 patients receiving temporary phrenic paralysis.

*Example (Case 9)* The patient was a 53 year old man who had a maximum breathing capacity of 79 liters before operation. After right temporary phrenic paralysis, the maxi-

TABLE 1

Ratio of  $\frac{\text{Walking Ventilation}}{\text{Maximum Breathing Capacity}}$  and Presence of Dyspnea in 98 Patients after the Pneumothorax Lung was Expanded

	RATIO BELOW .35 DYSPNEA NOT PRESENT	RATIO ABOVE .35 DYSPNEA WAS PRESENT
No fluid, or fluid not in sufficient amount, nor persisting sufficiently long to require repeated aspirations 60 patients	93 per cent	7 per cent
Fluid sufficient in amount and persisting sufficiently long to require repeated aspirations 38 patients	92 per cent	8 per cent

imum breathing capacity fell 21 liters, to 58 liters. Walking ventilation was 22 liters before operation, 21 liters after operation.

In our experience, temporary phrenic paralysis usually can be expected to lower the maximum breathing capacity 10 to 15 liters. Such a reduction is no handicap to the patient who has an initial maximum breathing capacity of 75 liters or more. When the maximum breathing capacity before phrenic operation is below 50 liters, however, such a loss of 10 to 15 liters may produce actual or imminent dyspnea.

*Example (Case 9)* The patient was a 35 year old woman whose ventilatory function tests yielded the following values:

	liters
August 1946—before right phrenic paralysis	46.1
August 1946—nerve injected with novocaine	33.1
August 1946—5 days after crushing nerve	23.1
October 1946—right temporary phrenic paralysis and pneumoperitoneum	28.1
January 1947—pneumoperitoneum absorbed	1
April 1947—motion returning to right hemidiaphragm	30.1
July 1947—motion returned to right hemidiaphragm	44.1

The patient had a maximum breathing capacity of 46 liters before phrenic paralysis. The operation was done on the right side, which, by fluoroscopy, appeared to contribute slightly more to the total ventilation than the left. After injecting the nerve with novocaine, the wound was closed and the maximum breathing capacity was redetermined and was found to be 33 liters. This was not considered too low and the wound was reopened and the nerve crushed. The reliability of this method of testing ventilation before actually crushing the nerve was demonstrated by the fact that the maximum breathing capacity was found to be 33 liters five days after the operation. Pneumoperitoneum was subsequently used to supplement the phrenic paralysis and resulted in further reduction of the maximum breathing capacity to 28 liters. At this level the patient was frequently slightly dyspneic even on strict bed rest. As this was considered undesirable, the pneumoperitoneum was soon abandoned. With absorption of the abdominal air, the maximum breathing capacity returned to 32

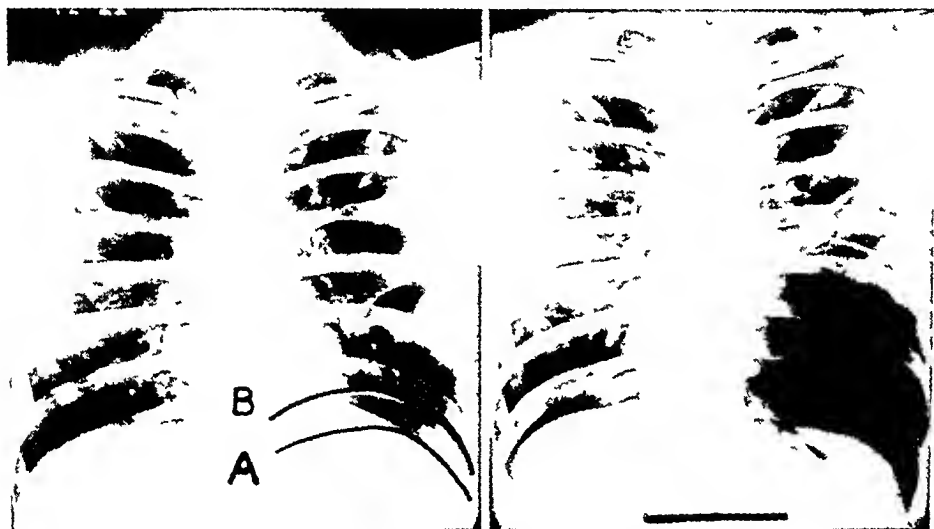


FIG 19 (Case 10) (Left) Before left temporary phrenic paralysis. Diaphragm level at A before operation. M B C, 141 liters, W V, not done.

With left temporary phrenic paralysis alone. Diaphragm level at B following operation. M B C, 129 liters, W V, not done.

FIG 20 (Case 10) (Right) With left temporary phrenic paralysis supplemented by pneumoperitoneum. M B C, 129 liters, W V, 26 liters, ratio, 20.

liters. As motion returned to the right hemidiaphragm, the maximum breathing capacity rose to 40 liters, and eventually to 44 liters, comparable to the pre-phrenic level.

From experience of this sort in two patients, we feel that phrenic paralysis should be done with extreme caution in patients with a maximum breathing capacity below 50 liters and especially so when the operation is to be performed on the side of better function.

### *Pneumoperitoneum*

As employed in our sanatorium, pneumoperitoneum seldom reduced the maximum breathing capacity more than 5 liters. This was the case whether the pneumoperitoneum was used alone or as a supplement to phrenic paralysis.

*Example (Case 10)* The patient was a 16 year old boy who had a left temporary phrenic paralysis which lowered his maximum breathing capacity from 141 liters to 129 liters (figure 19) Addition of pneumoperitoneum brought about no further change in the value for maximum breathing capacity (figure 20)

## DISCUSSION

The method described above for the evaluation of pulmonary function relies on careful fluoroscopy for estimation of the function of the individual lungs. The criticism can be raised that accurate determination of the breathing effort of each lung is not possible without differential bronchspirometry. In fact, Wright (7), while finding satisfactory correlation of bronchspirometric and fluoroscopic data in two-thirds of his total cases, feels that serious error may occur in individual patients. On the other hand, some clinicians question the reliability of differential bronchspirometry in individual cases because of the mechanical diffi-

TABLE 2

*Functional End Results in 123 Patients Subjected to Operation*

	MAXIMUM BREATHING CAPACITY BEFORE OPERATION		
	30 to 49 L	50 to 69 L	70 or more L
Studied by ventilatory method 123 patients	(6 patients studied)	(47 patients studied)	(70 patients studied)
Status after operation	1 died, 5 satisfactory	47 satisfactory	1 cripple, 69 satisfactory
Studied by differential broncho- spirometry 17 patients	(2 patients studied)	(8 patients studied)	(7 patients studied)
Status after operation	2 satisfactory	3 died, 5 satisfactory	7 satisfactory

culties involved in the procedure. Even the physiologists will not always quarrel with this statement.

In addition, the method described in the present communication utilizes only ventilatory tests and gives no information regarding oxygen intake and carbon dioxide output. These facts are of importance if the lung to be collapsed has a higher proportion of oxygen absorption in comparison to its ventilation. For example, a lung to be collapsed may be performing only 20 per cent of the total ventilation, yet may account for 40 per cent of the total oxygen absorption. This unfavorable situation does not occur often and was found only once in 26 patients who were studied preoperatively by differential bronchspirometry at Laurel Heights.

The value of a method is judged largely by the end results. One hundred and twenty-three patients, studied before thoracoplasty or resection, have come to operation and have been studied or observed postoperatively (table 2).

For analysis these patients have been divided into three groups according to the preoperative value for maximum breathing capacity. A value of 30 to 49

liters was classified as low, 50 to 69 liters as moderate, and 70 or more liters as high. It is the 6 patients in the 30 to 49 liter group and the 47 patients in the 50 to 69 liter group who constitute the real test of the method. On the basis of the preoperative ventilatory studies, it was predicted that all of the 123 patients could tolerate operation and would not be severely dyspneic when walking after operation. In only two cases was this prediction incorrect. One patient with a preoperative maximum breathing capacity of 36 liters died from respiratory failure after operation. A second patient had a maximum breathing capacity of 75 liters before operation which was reduced by thoracoplasty to 48 liters. Unfortunately her walking ventilation was 30 liters per minute and she became a respiratory cripple, unable to walk without severe dyspnea.

An additional small group of 17 patients was studied by differential bronchspirometry preoperatively, they were considered satisfactory risks for operation. Of these, 3 in the 50 to 69 liter group had marked dyspnea, continuing to death, after thoracoplasty. Not only are the end results in the ventilatory group satisfactory in themselves, but, in our hands, they compare favorably with those of the small group which was studied by differential bronchspirometry.

In our experience, these ventilatory studies, including careful fluoroscopy, are a sufficiently accurate means for evaluation of pulmonary function in all but the exceptional case. The simplicity of the method recommends its use where the more intricate physiological tests are not available. This is not to be construed as a disparagement of the procedure of differential bronchspirometry. Nevertheless, the reality must be accepted that most physicians and clinics, because of the time, costly equipment, and expert knowledge of pulmonary physiology required, cannot or will not use bronchspirometry.

#### SUMMARY

Certain simple tests of ventilatory function (maximum breathing capacity, walking ventilation), combined with careful fluoroscopy of the chest, can yield much information for evaluating the presence or imminence of dyspnea in patients with pulmonary disease. In cases where collapse measures are contemplated, these ventilatory tests assist in determining the patient's ability to tolerate a given procedure.

The apparatus for performing these tests of ventilatory function and the method are described. Cases illustrating the practical application of the tests are reported and end results in 123 patients after operation are analyzed.

#### SUMARIO

#### *Pruebas Sencillas de la Función Ventiladora para Empleo en el Sanatorio o la Clínica*

Ciertas sencillas pruebas de la función ventiladora (máxima capacidad respiratoria, ventilación ambulante), combinadas con la cuidadosa roentgenoscopia del tórax, pueden facilitar mucha información para apreciar la presencia o la inminencia de disnea en los enfermos con afecciones pulmonares. En los casos con-

siderados para medidas de colapso, esas pruebas de la aeración ayudan a determinar la capacidad del enfermo para tolerar un procedimiento dado

Describense el aparato necesario para ejecutar dichas pruebas de la función ventiladora y la técnica. Al presentar casos que demuestran la aplicación práctica del método, analizanse los resultados terminales en 123 enfermos operados

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# PHRENIC NERVE INTERRUPTION IN THE TREATMENT OF PULMONARY TUBERCULOSIS<sup>1</sup>

## II Complications and Sequelae of Phreniclasia

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### INTRODUCTION

In spite of a voluminous literature on temporary phrenic nerve interruption, there is relatively little reference to the complications and sequelae of the operation. The importance of knowledge concerning untoward effects, however, in particular the chance of prolonged or permanent loss of hemidiaphragmatic function, is well recognized (1-8).

### MATERIALS AND METHODS

The material for this study was derived from two sources

(a) 382 patients subjected to 516 phreniclasies at Trudeau Sanatorium between 1932 and September 1948 (9), and

(b) 156 patients and expatients previously treated with phreniclasia by physicians<sup>2</sup> and at sanatoriums<sup>3</sup> in and around Saranac Lake, N. Y.

All of the operations in the first group and most of those in the second were performed by one of four surgeons<sup>4</sup>. In those performed elsewhere, some details were made available by correspondence. Chest roentgenograms were available for review by the author in 92 per cent of the first group. Follow-up data were obtained wherever necessary by correspondence with the patients, attending physicians, and with other institutions.

Ninety-six of the first group and all of the second group, 252 patients in all, were personally interviewed and fluoroscoped by the author from one to eight times between March 1947 and September 1948. Readmitted patients and expatients back for a checkup or a visit provided most of the cases followed for two years or more after operation.

In those cases first seen long after phreniclasia, the decision that hemidia-

<sup>1</sup> From Trudeau Sanatorium and the Edward L. Trudeau Foundation, Trudeau, New York.

<sup>2</sup> Doctors Daniel M. Brumfiel, John N. Hayes, Henry W. Leetch, J. Woods Price, Francis B. Trudeau, and George E. Wilson, to whom the author is indebted.

<sup>3</sup> New York State Hospital for Tuberculosis, Ray Brook, New York, Northwoods Sanatorium, Saranac Lake, New York, Will Rogers Memorial Hospital, Saranac Lake, New York, Veterans Administration Hospital, Sunmount, New York, to the staffs of which the author is indebted.

<sup>4</sup> Phreniclasies by Doctors Edward S. Welles, Warner Woodruff, Carl G. Merkel, Saranac Lake, New York, and Winfield O. Kelley, Norwich, Connecticut, to whom the author is indebted for operative data. In every instance, so far as could be determined, the technique of the operation consisted of a single crushing of the main phrenic trunk or trunks with a smooth-faced clamp 1 mm. in width, plus section of all accessories found.

phragmatic paralysis had been effected was based upon reports of serial fluoroscopic examinations in the clinical record. The examinations were made at approximately monthly intervals and consisted in a record of the excursion, measured in millimeters, of each hemidiaphragm during both quiet and deep breathing in the erect position. Moreover, the response, normal or paradoxical, of each hemidiaphragm to an inspiratory sniff was also included. According to criteria now in general use, the paralyzed side differs from the unparalyzed side as follows: (a) no descent, or a paradoxical rise, on quiet inspiration, (b) limitation of descent on full inspiration after a forced expiration, and (c) paradoxical rise on inspiratory sniff.

It was originally planned to use these criteria in the series of patients examined personally. However, largely because of additional information gained by fluoroscopying the diaphragm with the patient in the recumbent position<sup>5</sup>, new criteria were developed and are outlined in table 3.

Diaphragmatic excursion on both quiet and deep breathing tended to be greater in the recumbent than in the erect position. This was true regardless of

TABLE 1  
*Range of Normal Hemidiaphragmatic Excursion in 252 Patients*

POSITION	TOTAL EXCURSION IN CM	
	Quiet breathing	Forced breathing
Erect	0.5 to 5.0	1.0 to 10.0
Recumbent	1.0 to 5.0	2.0 to 12.5

whether one hemidiaphragm was paralyzed, merely weak, or normal. Of the 252 patients fluoroscoped, 73 showed at least 1 cm. greater excursion in the recumbent than in the erect position on all examinations, 10 showed the reverse, serial observations varied in 9, and in the remainder the difference was less than 1 cm. or the observations were inconclusive. The range of normal hemidiaphragmatic excursion in these 252 patients may be seen in table 1.

True rise above the expected position of quiet expiration of a totally paralyzed hemidiaphragm was observed in 14 cases in the recumbent but not in the erect position. Frequently rise was observed in both positions, but in no instance was it present in the erect position only.

The diaphragmatic response to a short inspiratory sniff very frequently was more nearly normal, *e g*, prompt descent, in the recumbent than in the erect position during the period when return of function was being observed, or from five to eighteen months after phrenicosis (see table 2).

In other words, there were frequent instances where fluoroscopy in the recumbent position yielded considerable additional information. For instance, in spite of the presence of the accepted criteria for hemidiaphragmatic paralysis in the erect position, slight but definite evidence of beginning return of function

<sup>5</sup> Suggested to the author by Dr. George W. Wright.



was found in the recumbent position in 12 cases. This was presumably due to the freer diaphragmatic excursion seen in the recumbent position. On the other hand, 4 patients with recent phreniclasia revealed the following findings. There was some descent of the hemidiaphragm on quiet inspiration, almost normal movement on deep breathing, paradoxical response to sniff, and no "rise" in the erect position. In the recumbent position there was, in addition to the paradoxical response to sniff, no motion on quiet breathing and almost none on deep breathing, and a very definite "rise" above the level of quiet expiration. One patient in fact received an immediate repeat phreniclasia because of the absence of convincing evidence of paralysis on fluoroscopy in the erect position. The fluoroscopic observations were unchanged after the repeat operation. While again virtually fixed in the position of quiet expiration in the recumbent position, the hemidiaphragm continued to show considerable motion on both quiet and deep breathing in the erect position.

TABLE 2

*Response of Previously Paralyzed Hemidiaphragms to a Sharp Inspiratory Sniff in the Erect and Recumbent Positions 5 to 18 Months after Phreniclasia*

	NUMBER	PER CENT
Paradoxical in erect but not in recumbent position*	33	66.5
Paradoxical in both positions	16	33.0
Paradoxical in recumbent but not in erect position	1	0.5
Total cases	50	100.0

\* In 7 of these cases there was no movement up or down in the recumbent position.

The criteria for paralysis, muscular weakness, and normal behaviour of hemidiaphragms, as finally used in the author's series, are outlined in table 3. The difference between apparent and true elevation or "rise" of the hemidiaphragm must be emphasized. Usually the recently paralyzed muscle becomes more or less fixed in the position of quiet expiration. This leads to the appearance of "rise" on the routine chest roentgenogram taken at full inspiration. In some cases, presumably due to contracting intrapulmonary diseased tissue, a paralyzed hemidiaphragm will actually rise above the level of quiet expiration, occasionally to as much as two posterior interspaces above the other side. At the other extreme it may remain fixed somewhere near the position of full inspiration, presumably because of pleural or peritoneal adhesions.

Predominance of costal breathing presented a technical problem, especially in young women. If the excursion of an ostensibly normal hemidiaphragm from full expiration to full inspiration did not traverse the normal range of about two full posterior interspaces, the examination was considered incomplete and was repeated after one week's practice in diaphragmatic breathing. Instruction in diaphragmatic breathing at the fluoroscope, however, usually made a re-examination unnecessary. Binding or holding the chest to limit costal breathing

is a method which, in the writer's experience, did not bring about full use of the diaphragm. Serial examinations made at intervals from a few days to three or four weeks showed surprisingly little variation in diaphragmatic excursion when abdominal breathing was enforced.

Another problem occasionally met was the paralysis of a hemidiaphragm in one segment with normal response elsewhere. This was probably a consequence

TABLE 3

*Suggested Criteria for Paralyzed, Weak (Atrophic), and Normal Hemidiaphragms\**

FLUOROSCOPIC OBSERVATION	HEMIDIAPHRAGMATIC EXCURSION OBSERVED IN		
	Total paralysis	Muscular weakness or atrophy	Normal
Apparent "rise" failure to descend to the position of full inspiration	Present	Present	Usually none
True elevation or "rise" upward displacement from the position of quiet expiration	Up to 2 posterior interspaces higher but frequently absent	Usually absent, occasionally present	None
Response to quiet breathing in the recumbent position	† Absent or paradoxical	Present but reduced	10 to 50 mm and usually equal to other side
Response to forced diaphragmatic breathing in both erect and recumbent positions	Reduced 50% or more when compared to opposite side. Rarely paradoxical	Reduced	60 to 125 mm and roughly equal to opposite side
Response to inspiratory sniff in the erect position	Paradoxical	Paradoxical, lag or normal	Normal descent
Response to inspiratory sniff in the recumbent position	† Paradoxical	Lag or normal	Normal descent

\* Based upon the author's experience in the 252 cases examined fluoroscopically

† The most significant signs of total paralysis

of failure to interrupt a secondary phrenic nerve trunk or major accessory. Persistent total paralysis or severe dysfunction of a part of a hemidiaphragm was seen several times, occasionally years after an exaeresis.

Paralysis known to have lasted three months or less was presumed to have been due to incomplete nerve crushing and was classified as an inadequate or "unsatisfactory" phreniclasia for two reasons.

1. Hemidiaphragmatic motion was usually reduced rather than abolished in these cases.

2 From a technical standpoint, a total paralysis of less than 120 days seems impossible since nerve tissue regenerates at from 0.25 to 2.5 mm per day (10) and the distance from the point of nerve crush to the dome of the diaphragm is from 300 to 400 mm in the adult. Using the fastest rate and shortest distance, the minimum elapsed time would therefore be 120 days.

#### FAILURE TO OBTAIN PARALYSIS FOLLOWING PHRENICLISIS

##### *Incidence and Relation to the Finding and Sectioning of Accessory Phrenic Nerves*

The incidence of failure to obtain hemidiaphragmatic paralysis following phrenic nerve crush has been reported in various series as follows: 0.3 per cent (11), 1.5 per cent (2), 5 per cent (6), 12.8 per cent (12).

TABLE 4

*Incidence of Failure to Obtain "Satisfactory" Paralysis after Phreniclsis at Trudeau Sanatorium 1932-1947*

OUTCOME	PHRENICLISIS OPERATIONS									
	First		Second		Third		Fourth		Total	
	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent
"Satisfactory" paralysis										
Lasted over 3 months	330		95		11		1		437	
Inadequate paralysis										
a Lasted 3 months or less	12	9	4	14	1	27	0	—	17	11
b No paralysis obtained	19		11		3		0	—	33	
Totals	361		110		15		1		487	

In the 487 phreniclses performed on 361 patients at Trudeau Sanatorium between 1932 and November 1947, the incidence of failure to obtain "satisfactory" paralysis, or a paralysis of over three months' duration, was 9 per cent with the first operation, 17 per cent with the second, and 27 per cent with the third (table 4).

The percentages of failure as shown in table 4 represent 50 failures to obtain "satisfactory" paralysis in 38 different patients. In 22 of these 38 patients no attempt to recrush the nerve was made for various reasons which were not always clear in the records. Of the other 16 patients on whom a second attempt to obtain paralysis after initial failure was made, 6 were successful. The incidence of failure to produce any successful paralysis in the series is therefore slightly less than 9 per cent. It is of interest that in each of the 6 successes after previous failure, one or more accessory nerves were sectioned on the repeat operation, when accessory nerve data were recorded.

It has been strongly emphasized (13) that a careful search for accessory phrenic nerve fibres is essential to consistent success in obtaining hemidiaphragmatic

paralysis with phrenicectomy. Table 5 shows this relationship in 187 consecutive phrenicectomies at Trudeau Sanatorium.

At initial operation, failure to obtain satisfactory paralysis was observed in 11 per cent of those in which no accessory nerve was found, whereas failure was observed in only 5 per cent of those in which at least one accessory nerve was sectioned. At repeat operation failure was somewhat greater (11 per cent) when accessories were sectioned than when none were found (10 per cent), but the incidence of previous permanent interruption of accessories in the latter group was high.

When the operative note contained no reference to accessory nerves, the surgeon may be presumed to have been less concerned about their possible presence.

TABLE 5

*Relation of Success in Obtaining "Satisfactory" Hemidiaphragmatic Paralysis to the Finding and Sectioning of Accessory Phrenic Nerves*

1 OR MORE ACCESSORY PHRENIC NERVES	INITIAL OPERATIONS			REPEAT OPERATIONS		
	Total	No paralysis or 'inadequate' paralysis, i.e., lasted 3 months or less		Total	No paralysis or 'inadequate' paralysis, i.e., lasted 3 months or less	
		Number	Per cent		Number	Per cent
Found*	113	7	5	14	2†	14
Not found	111	12	11	51	5‡	10
Complete operative data available	254	19		65	7	
No data on accessories	107	12	11	61	12	19
Total operations	361	31	9	126	19	15

\* All accessories found were sectioned.

† In spite of the sectioning of accessory nerves, these two repeat operations were again failures after a previous failure.

‡ The surgical technique of repeat operations after a previous success usually did not include a careful search for accessory nerves.

and importance. The high (11 per cent) incidence of failure to obtain satisfactory paralysis in 107 such cases therefore lends further weight to the importance of a thorough search for accessory nerves at initial operations.

#### THE OPERATIVE COMPLICATION OF PHRENICCLASIS

The following operative complications have been reported in the literature (2, 5, 11, 13, 14): injury to the thoracic duct, injury to the vagus nerve, injury to the cervical sympathetic nerves, injury to the brachial plexus, traumatic pneumothorax, and injury to the recurrent laryngeal nerve.

In the 487 phrenicectomies performed at Trudeau Sanatorium between 1932 and November 1947, 32 operative complications were encountered and are outlined in table 6.

Lobular atelectasis was a roentgen finding without significant accompanying

symptoms In addition, initial and final therapeutic results observed after phreniclasia in the 16 such cases were practically identical to the results previously reported in the group as a whole (9)

The single instance of gastric dilatation complicating left-sided phreniclasia was in direct contrast to a rather high incidence previously reported (15)

One operation, not recorded as a failure, was stopped when pus welled into the wound from a suppurating tuberculous lymph node

The incidence of all operative complications was therefore 6.5 per cent Only 0.4 per cent of these were fatal, i.e., 2 far advanced "desperate risk" cases

TABLE 6  
*Complications of Phreniclasia at Trudeau Sanatorium*

OPERATIVE COMPLICATIONS*	NUMBER OF CASES	PER CENT
Injury to cervical sympathetic nerve	4	0.8
Laceration of thoracic duct	2	0.4
Total technical errors	6	1.2
UNTOWARD REACTIONS TO HEMIDIAPHRAGMATIC PARALYSIS†	NUMBER OF CASES	PER CENT
Dyspnea, severe, and death same day‡	1	
death 31 days later	1	0.4
Dyspnea, moderate	7	1.4
Lobular atelectasis, severe	2	
mild to moderate	14	3.3
Severe gastro-intestinal symptoms due to gastric dilatation following left-sided operation	1	0.2
Total untoward reactions to hemidiaphragmatic paralysis	26	5.3
Total complications	31	6.5

\* Five of the six operative complications occurred at repeat phreniclasia, presumably because of the difficulties of dissection through scar tissue

† Twenty-five of the 26 untoward reactions to hemidiaphragmatic paralysis followed initial phreniclasia

‡ Operation performed on patient in bed in a desperate attempt to stop massive recurrent hemorrhage

None of the other complications was considered serious In a survey of 4,697 cases (16), "serious" complications occurred in 1.2 per cent, which included 0.5 per cent deaths

#### THE EFFECT OF HEMIDIAPHRAGMATIC PARALYSIS ON THE COUGH MECHANISM AS OBSERVED FLUOROSCOPICALLY

Opinion has been divided on the effect of hemidiaphragmatic paralysis on the cough mechanism Cough and expectoration seem to be improved clinically in some cases On the other hand, some observers believe that expectoration is made more difficult, and that there is a tendency for secretions to be retained

within the lung and bronchi. The limited data available on experimental animals (17) and on humans (18) tend to support the contention that expectoration is impaired by phrenic nerve interruption.

In the course of studying the behaviour of the paralyzed hemidiaphragm fluoroscopically, patients were asked to give a hard cough while in both the erect and recumbent positions. The behaviour of the unparalyzed hemidiaphragm on coughing was as follows. During the initial inspiration the diaphragm usually descends slightly and the glottis closes. Then as the glottis is opened, the dia-

TABLE 7

*Relation of Age and Sex to Duration of Hemidiaphragmatic Paralysis after Phrenicclasis*

	NUMBER OF CASES	DURATION OF MONTHS		
		Mean	Median	Range
<i>Initial phrenicclases</i>	190	7 10	6 50	3½ to 18
Sex				
Males	97	7 13	6 50	
Females	93	7 08	6 50	
	—			
	190			
Age				
15 to 25	77	6 61	6 00	
26 to 40	100	7 47	7 00	
41 to 56	13	7 80	7 00	
	—			
	190			
<i>Repeat phrenicclases</i>	38	8 15	7 40	3½ to 18
Sex				
Males	18	8 20	7 50	
Females	20	8 10	7 30	
	—			
	38			
Age				
15 to 25	14	8 36	8 00	
26 to 40	20	8 10	7 50	
41 to 56	4	9 30	9 50	
	—			
	38			

phragm abruptly rises coincident with the expulsive effort produced by the strong contraction of abdominal and thoracic muscles. This sudden rise during the expulsive phase of cough was a very constant observation in both positions except in advanced emphysema when both leaves of the diaphragm usually descend slightly, and in the presence of pneumothorax, when the homolateral hemidiaphragm frequently remains immobile.

In the erect position the paralyzed hemidiaphragm also rises during the expulsive phase of cough, in the manner of the unparalyzed side, although occasionally this is accomplished after a slight lag, asynchronously, or in a flabby fashion.

In the recumbent position, on the other hand, the paralyzed hemidiaphragm shows a distinctly paradoxical descent during the expulsive phase of cough while the normally functioning side is rising. After the force of the cough is expended, the paralyzed half returns to its former level. This observation was made on 45 of 48 patients with total hemidiaphragmatic paralysis produced by a recent phrenic nerve crush. As function began to return, this phenomenon usually disappeared although it was observed in 14 of 132 cases during the period of muscular weakness after nerve regeneration.

#### THE DURATION OF HEMIDIAPHRAGMATIC PARALYSIS FOLLOWING PHRENICLASIS

Of 361 patients subjected to one or more operations of phrenicectomy, there were 437 "satisfactory" paralyses (table 4). In 190 initial and 38 repeat operations, each with proved return of function based upon reports of erect fluoroscopy only, follow-up data were sufficiently complete to permit a fairly accurate determination of the duration of paralysis.

In table 7 it may be seen that the range in the duration of paralysis was three and one-half to eighteen months. This has been previously reported as from three to eighteen months (14, 19) with an average of six to nine months (19). Table 7 further shows that there is a tendency for the mean and median duration to be longer after repeat operation and a slight tendency to be longer in the older age group. There was little difference in the figures between men and women. In making this study it was further noted that if no return of hemidiaphragmatic function had been observed by about 18 months after operation, the paralysis persisted and presumably became permanent.

#### THE DEGREE OF RETURN OF HEMIDIAPHRAGMATIC FUNCTION FOLLOWING PHRENICLASIS

There are only limited data on the incidence of permanent paralysis after phrenicectomy. The following figures have been previously reported: 6 to 8 per cent (16), 10 per cent (7, 8, 13), 11 per cent (6), 12.3 per cent (2), and 24 per cent when supplemented with pneumoperitoneum (20). There is even less evidence on partial permanent disability. The only specific reference found states: "In 54.8 per cent the function was moderately impaired either partly because of the lack of nerve regeneration or because of fixation of the diaphragm by adhesions" (6).

Out of 336 patients with 437 "satisfactory" paralyses (table 4), 312 were followed long and carefully enough either at the sanatorium or by the attending physicians after discharge to establish the fact that either nerve regeneration had taken place or that permanent total paralysis had resulted, on the basis of fluoroscopic examinations in the erect position.

In the process of fluoroscoping patients with previous phrenicectomy, the writer gained the impression that the figures on permanent total paralysis after phrenicectomy, as revealed in table 8 and in previous reports, not only were low but did not tell the whole story of persistent hemidiaphragmatic disability. In other words, quite a few hemidiaphragms revealed fluoroscopic evidence of muscular

weakness or atrophy years after disappearance of the evidence of total paralysis. As a consequence, an effort was made to fluoroscope as many subjects as possible who had had one or more successful paralyzes.

In a series of 252 such individuals, the time elapsed after the most recent phrenic nerve crush varied from a few hours to over 15 years. Serial examinations

TABLE 8

*Incidence of Permanent Paralysis after Phreniclasia*

*From the Records of all Trudeau Sanatorium Patients, 1932-1947, with Sufficient Follow-up following Phreniclasia to Permit an Accurate Determination*

HEMIDIAPHRAGMATIC FUNCTION	PHRENICLASIS				
	Single		Multiple		
	Number	Per cent	Number	Per cent	
<i>Regained</i>					
a) Interval known	190		38		
b) Interval unknown	44		26		
	—		—		
c) Total	234	96	64	93	
Permanent Paralysis i e , <i>not regained</i> 2 or more years after last operation	9	4	5	7	
Total	243	100	69	100	312

TABLE 9

*Permanent Hemidiaphragmatic Disability Observed Fluoroscopically by the Author Two Years or More after "Satisfactory" Phreniclasia*

PERMANENT HEMIDIAPHRAGMATIC DISABILITY	PHRENICLASIS				
	Total Cases	Single		Multiple	
		Number	Per cent	Number	Per cent
1 None or practically none	78	56	62	22	48
2 Slight	19	11	12	8	17
3 Moderate to severe (50% or more)	29	18	20	11	24
4 Total paralysis	10	5	6	5	11
Total cases	136	90		46	

again revealed that improvement in hemidiaphragmatic function was observed up to but seldom after 18 months after phreniclasia.

In table 9 may be seen the incidence and severity of disability observed in all 136 cases examined 2 years or more after their last paralyzing phreniclasia. The cases were derived from the entire patient and outpatient population in Saranac Lake and environs. The only cases excluded were those with no or inadequate paralysis after all phrenicclases performed, and those with less than a 24 months'



interval between the most recent operation and the latest fluoroscopic examinations. Any paralysis of 3 months or less duration was not considered as a successful phreniclasia for the purposes of this study. The terms "slight," "moderate," and "severe" represent rough evaluations of disability ranging from normal function on the one hand and total paralysis on the other. "Moderate" disability was arbitrarily defined as at least 50 per cent loss of hemidiaphragmatic function, attributable as clearly as possible to muscular weakness or atrophy.

TABLE 10

*Relation of the Elapsed Time after Phreniclasia and the Degree of Hemidiaphragmatic Disability Observed on Fluoroscopic Examination*

INTERVAL BETWEEN LAST PHRENICLASIA AND LAST FLUOROSCOPY	TOTAL NUMBER OF CASES	INCIDENCE OF 50 TO 100 PER CENT LOSS OF HEMIAPHRAGMATIC FUNCTION TWO YEARS OR MORE AFTER LAST PHRENICLASIA	
		Number	Per cent
24 to 35 months	51	16	31
36 to 47	26	7	27
48 months or more	59	16	27
Total	136	39	29

TABLE 11

*Relation of Side of Operation and Age and Sex of Patient to Incidence of Permanent Hemidiaphragmatic Disability*

FACTOR	TOTAL NUMBER OF CASES	50 TO 100 PER CENT LOSS OF HEMIAPHRAGMATIC FUNCTION ATTRIBUTABLE TO PHRENICLASIA AND PERSISTING FOR TWO YEARS OR MORE AFTER LAST OPERATION	
		Number	Per cent
<i>Side of Operation</i>			
Left	61	22	36
Right	75	17	23
<i>Sex</i>			
Male	68	21	31
Female	68	18	27
<i>Age Group</i>			
14 to 35	104	26	25
36 to 56	32	13	41

only. The disabling effect of adhesions produced by pleurisy with effusion, pneumothorax with effusion, or empyema, and the limiting effect of a later thoracoplasty, were carefully considered. An appropriate part of any hemidiaphragmatic disability observed short of total paralysis ascribable to these factors was then deducted from the disability ascribed to phreniclasia.

Twenty-six per cent of patients with single phreniclasies and 35 per cent with multiple phreniclasies showed a persistent 50 per cent loss of hemidiaphragmatic mobility, presumably attributable to previous phreniclasia.

It is of interest that the figures for permanent total paralysis in the series examined by the author were 6 per cent with single and 11 per cent following multiple phreniclasies. These figures are felt to be more nearly accurate than those derived in table 8 from sanatorium and other physicians' records, which were based on fluoroscopy in the erect position only.

In table 10 it may be seen that from a statistical standpoint there is only a very slight chance of further return of function more than two years after the last phreniclasia. The incidence of 50 to 100 per cent loss of hemidiaphragmatic function was roughly the same in three groups of patients. In those examined in the third year it was 31 per cent. In those patients examined in the fourth year and in those examined in the fifth to fifteenth year after their last "satisfactory" phreniclasia, the incidence was 27 per cent.

It is apparent from table 11 that the incidence of permanent disability was significantly higher in the older age group and in those with left-sided phreniclasia. The patient's sex made only a slight difference.

TABLE 12

*Relation of the Sectioning of Accessory Phrenic Nerves to Incidence of Permanent Hemidiaphragmatic Disability Following Phreniclasia*

ACCESSORY PHRENIC NERVES FOUND AND SECTIONED	TOTAL NUMBER OF CASES	50 TO 100 PER CENT LOSS OF HEMIDIAPHRAGMATIC FUNCTION ATTRIBUTABLE TO PHRENICLASIA AND PERSISTING FOR TWO YEARS OR MORE AFTER LAST OPERATION	
		Number	Per cent
One or more	48	13	27
None	25	6	24
Complete operative data on accessory nerves not available	63	20	32
Total	136	39	

In table 12 it is seen that the sectioning of accessories did not materially change the incidence of persistent hemidiaphragmatic disability in the 73 cases in which complete operative data and fluoroscopic studies two years or more after phreniclasia were both available.

## COMMENT

It would appear that the paradoxical behaviour of the totally paralyzed hemidiaphragm when the patient coughs in the recumbent position should impair the ability to expectorate. By the same token, patients should be able to expectorate more readily in the erect position. It has not been possible to verify this hypothesis clinically as yet.

The explanation of this observation that the totally paralyzed hemidiaphragm responds paradoxically to cough in the recumbent and not in the erect position is not entirely clear.

If at the time of occurrence of this phenomenon the sum of thoracic and ab-

dominal pressures results in a higher supradiaphragmatic pressure in the recumbent than in the erect position, this paradoxical descent of a flaccid hemidiaphragm only in the recumbent position may be clarified. This change in relative pressures is presumed to occur for two reasons (a) the abdominal cavity is relatively larger in the recumbent than in the erect position because of the normal upward displacement of the entire diaphragm in the recumbent position and the diaphragm is therefore less readily compressed in this position, and (b) while the postural abdominal muscles tend to relax upon change from the erect to the recumbent position, the respiratory thoracic muscles are unaffected by any change in position.

Improvement in the mobility of previously paralyzed hemidiaphragms has been observed fluoroscopically in isolated cases after as much as four years (21). This observation was not made in this series but statistically there was a slight additional gain in function in the third year after the last phrenicectomy.

The most reliable evidence of hemidiaphragmatic paralysis appears to be an absence of motion on quiet breathing and/or a paradoxical response to an inspiratory sniff, when the patient is in the recumbent position. It is quite important that the sniff be a sharp, definite, inspiratory effort.

Paradoxical rise of one hemidiaphragm on inspiratory sniff with the patient in the erect position, however, has been heretofore considered the best test for paralysis. This finding indicates only weakness of the hemidiaphragm, in the writer's experience. Four patients, for instance, who had never had a phrenic nerve interruption, had paradoxical movement of one leaf of the hemidiaphragm when they were in the erect position. In addition, a paradoxical response to the sniff test in the erect position may persist for months after nerve regeneration has definitely occurred, as evidenced by clear-cut descent of the diaphragm on quiet inspiration, especially with the patient in the recumbent position. On the other hand, no descent of the hemidiaphragm on quiet breathing was observed in either position if a paradoxical response to the sniff test occurred when the patient was in the recumbent position.

#### SUMMARY AND CONCLUSIONS

- 1 The incidence of permanent total paralysis was 6 per cent after single and 11 per cent after multiple "satisfactorily" paralyzing phrenicectomies. Permanent loss of roughly one-half or more of hemidiaphragmatic function, attributable to phrenicectomy, was 26 per cent after single and 35 per cent after multiple operations. This incidence was significantly higher in patients past 35 and in left-sided operations.

- 2 The incidence of failure to obtain "satisfactory" hemidiaphragmatic paralysis with phrenicectomy was 9 per cent for the first operation, 14 per cent for the second, and 27 per cent for the third.

- 3 Success in obtaining "satisfactory" paralysis was found to be directly related to the finding and sectioning of accessory phrenic nerves.

- 4 The behavior of the paralyzed hemidiaphragm during the expulsive phase of cough was found to differ in the erect and recumbent positions.

5 The duration of temporary hemidiaphragmatic paralysis following phreniclasia was found to vary from three and one-half to eighteen months, with a mean and median duration between six and one-half and nine and one-half months

6 The 65 per cent operative complications of phreniclasia and untoward reactions to hemidiaphragmatic paralysis were minor, except in two fatal cases (0.4 per cent), only one of which may be considered a direct complication of phreniclasia

#### SUMARIO Y CONCLUSIONES

##### *La Interrupción del Frénico en el Tratamiento de la Tuberculosis Pulmonar*

##### *II Complicaciones y Secuelas de la Freniclasia*

1 La incidencia de parálisis total permanente llegó a 6 por ciento cuando las freniclasias "satisfactoriamente" paralizantes fueron únicas y a 11 por ciento cuando fueron múltiples. La pérdida permanente de aproximadamente la mitad o más de la función hemidiafragmática, imputable a la freniclasia, representó 26 por ciento después de las primeras y 35 por ciento después de las segundas, siendo la incidencia significativamente mayor en los enfermos de más de 35 años y en las operaciones en el lado izquierdo.

2 La incidencia de fracasos en la obtención de parálisis hemidiafragmática "satisfactoria" fué de 9 por ciento para la primera operación, 14 por ciento para la segunda y 27 por ciento para la tercera.

3 El éxito en la obtención de parálisis "satisfactoria" resultó hallarse directamente enlazado con la localización y resección de los nervios frénicos accesorios.

4 La duración de la parálisis hemidiafragmática temporal consecutiva a la freniclasia varió de tres meses y medio a dieciocho meses, con una duración media y mediana de seis meses y medio a nueve meses y medio.

5 El 65 por ciento de complicaciones operatorias de la freniclasia y de reacciones adversas a la parálisis hemidiafragmática fueron de importancia secundaria, excepto en dos casos letales (0.4 por ciento), sólo uno de los cuales puede considerarse como complicación directa de la freniclasia.

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# PHRENIC NERVE INTERRUPTION IN THE TREATMENT OF PULMONARY TUBERCULOSIS<sup>1</sup>

## III The Effect of a Paralyzed Hemidiaphragm on the Results of Homolateral Thoracoplasty

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### INTRODUCTION

A recent survey has shown that after a single paralyzing phrenicectomy, while there is only a 6 to 10 per cent chance of total permanent paralysis, there is a 26 per cent chance of permanent loss of at least half the function of the hemidiaphragm (1). The chance of this partial disability was further found to rise to 35 per cent when a second phrenicectomy was successful in paralyzing the hemidiaphragm, and to 41 per cent in all patients past 35 years of age.

The fact that thoracoplasty may be later indicated in patients presenting indications for phrenicectomy is well known. For instance, by the end of 1947 subsequent homolateral thoracoplasty had been performed in 15 per cent of all patients treated with phrenicectomy at Trudeau Sanatorium from 1932 through 1944. Although a paralyzed hemidiaphragm has been considered a contraindication to homolateral thoracoplasty by several observers (2 to 8) details on actual experience in this situation have not been found in the literature.

### MATERIALS AND METHODS

The material for this study consisted of 103 patients of Trudeau Sanatorium treated with thoracoplasty before December 31, 1944. All Trudeau Sanatorium patients treated with thoracoplasty after a preceding phrenic nerve interruption provided 55 of these cases<sup>2</sup>; the other 48 consisted of all other patients treated with thoracoplasty at Trudeau Sanatorium from the first case in 1927.

The preoperative, operative, postoperative, and follow-up data in these cases were derived from the Sanatorium records and from correspondence with various attending physicians, surgeons, other institutions, and the patients themselves.

These 103 thoracoplasty cases were divided into two main groups, according to the functional status of the diaphragm at the time of the first stage of thoracoplasty.

*Normal diaphragm at the time of thoracoplasty.* Sixty-two patients had normal diaphragmatic function at the time of thoracoplasty. In 48 of these, the phrenic nerve had never been interrupted; in the other 14, there was satisfactory fluoroscopic evidence of return of hemidiaphragmatic function after a previous phrenic nerve interruption.

<sup>1</sup> From Trudeau Sanatorium and the Edward L. Trudeau Foundation, Trudeau, New York.

<sup>2</sup> Twenty-eight of these patients had thoracoplasty performed subsequent to their discharge from Trudeau Sanatorium.

*Partial or total homolateral hemidiaphragmatic paralysis at the time of first stage thoracoplasty* Forty-one patients had some degree of impairment of hemidiaphragmatic function at the time of thoracoplasty. In 27, the paralysis was total, including 13 exsireses<sup>3</sup>, in the other 14, fluoroscopy revealed at least partial disability before the first stage. The fluoroscopic data on these 14 cases unfortunately were insufficient to permit a clear distinction between paralysis and muscular

TABLE 1

*Comparability of Two Series of Thoracoplasties Performed with and without a Disabled Homolateral Hemidiaphragm*

	PARTIAL OR TOTAL PARALYSIS AT TIME OF FIRST STAGE THORACOPLASTY			NO PRIOR PHRENIC NERVE INTERRUPTION OR HEMI-DIAPHRAGMATIC FUNCTION HAD BEEN REGAINED BEFORE FIRST STAGE THORACOPLASTY
	Became Permanent*	Temporary or Presumably Temporary†	Total	
Total Cases 103	19	22	41	62
Preoperative Data				
Age				
Range	26 to 50	24 to 50	24 to 50	20 to 63
Mean and Median	33	33	33	33
Sex				
Males	58 %	48 %	54 %	40 %
Extent Far Advanced	58 %	48 %	54 %	44 %
Endobronchial tuberculosis found on bronchoscopy (48 different patients examined)	36 %	35 %	36 %	33 %
Operative Data				
Average number of stages	2.4	2.6	2.5	2.5
Average number of ribs resected	7.7	7.7	7.7	7.5
Year of operations				
Range	1928-1944	1935-1944	1928-1944	1932-1944
Mean and median	1935	1939	1937	1939
Postoperative Data				
Years of follow-up of living patients				
Mean	9.6	7.7	8.4	7.3
Median	8.2	7.5	7.8	7.0

\* 13 intentional due to exsiresis and 6 unintentional following phrenicclasis

† Phrenicclasis with function ultimately regained in 18, no postthoracoplasty fluoroscopic studies available in 4

weakness. These 41 cases were further subdivided into *postthoracoplasty return of hemidiaphragmatic function* (22 cases) and *permanent homolateral paralysis* (19 cases).

These two series of cases were then examined with regard to various factors which might interfere with the accuracy of a statistical comparison (table 1)

<sup>3</sup> All performed before 1934

It was found that the essential differences between the two main groups were that in those with a paralyzed hemidiaphragm before surgery there was a higher prevalence of far advanced disease, and that the thoracoplasties were performed in earlier years chronologically

The subdivision with disability ultimately determined to be permanent included 13 exaireses and hence contained a preponderance of the earlier thoracoplasties, since the last exairesis in this series was performed in 1934. Exclusion of these 19 cases left 22 cases which, with regard to the attributes considered in table 1, were comparable to the series of 62 patients with a normally functioning diaphragm at the time of thoracoplasty

### RESULTS

In table 2 may be seen the incidence of immediate postoperative roentgenographic spread of disease and of generalized cloudiness throughout the lung under collapse interpreted as "atelectasis" or airlessness plus congestion. The latter

TABLE 2

*Incidence of Immediate Postoperative Thoracoplasty Complications in 103 Patients with and without a Disabled Homolateral Hemidiaphragm*

	PARTIAL OR TOTAL PARALYSIS	NO PARALYSIS
Total Cases 103	41	62
Spread of disease after one or more stages		
Homolateral	2	1
Contralateral	4	6
Bilateral	3	6
Total	9 (22%)	13 (21%)
Homolateral "atelectasis" after one or more stages	4 (10%)	1 (1.6%)

complication was diagnosed only when there was an associated shift of the mediastinum toward the cloudyside. Intrapleural and extrapleural effusions, which may also cause general cloudiness, were excluded on the basis of the position of the heart and mediastinal structures.

It will be noted that there was little difference in the incidence of postoperative spread of disease in the two series.

The incidence of homolateral atelectasis, however, was 10 per cent in the group with a disabled homolateral hemidiaphragm at the time of surgery, whereas it was only 1.6 per cent in the group with a normally functioning diaphragm. Unfortunately, preoperative bronchoscopy had not been performed on any of the patients in whom this complication was diagnosed.

In table 3 may be seen the details of late therapeutic results after thoracoplasty in the same series of patients. Results were classified as "satisfactory" and "poor." "Satisfactory" was applied to those cases which recovered after thoracoplasty, either promptly (within one year) or slowly (within two years).



and then remained well and working, cavities closed<sup>4</sup> and sputum negative for *M tuberculosis*<sup>5</sup> for three years after the last stage<sup>6</sup>

"Poor" results were defined as (1) immediate operative deaths, (2) deaths from progressive tuberculosis within three years, (3) lapse into a state of chronic tuberculosis with "positive sputum" and/or persistent cavitation and/or severe respiratory embarrassment, (4) initial success, but with a significant relapse in one or both lungs within three years after the last thoracoplasty stage. One patient who died of a cause other than tuberculosis and 4, in whom postthoracoplasty follow-up data of at least three years' duration were not available, were excluded from statistical analysis but were included in computing the margin of error.

The incidence of "satisfactory" results in the patients with a normal homolateral hemidiaphragm was  $73 \pm 2$  per cent, while in the entire group with a disabled homolateral hemidiaphragm it was  $56 \pm 1$  per cent.

It was further observed that approximately the same percentage of "satisfactory" results was obtained in the group with permanent paralysis ( $58 \pm 0$  per cent) as in the group with temporary or presumably temporary paralysis ( $55 \pm 5$  per cent).

#### DISCUSSION

While immediate postthoracoplasty spread of disease was apparently unrelated, there was a definite tendency for both postoperative atelectasis and poor late results to occur in patients with preoperative evidence of a disabled homolateral hemidiaphragm.

It is not certain how much of this difference in late results after thoracoplasty may be attributed to the condition of the diaphragm at the time of operation, since so many variables enter into the picture. On the other hand, the difference in the two series is felt to be significant in spite of the limited number of cases. It should be pointed out, however, that the group with permanent paralysis is not wholly comparable to the other two groups because the mean year in which thoracoplasties were performed was three years earlier.

From a theoretical standpoint it is actually surprising that atelectasis did not occur more frequently in the presence of hemidiaphragmatic paralysis. During the period of decostalization and pain following a thoracoplasty stage, the burden of partial or total abolition of the costal component of breathing is thereby added to a lung, the ventilatory function of which is already impaired by partial or total hemidiaphragmatic paralysis. Pooling of secretions is probably also promoted in this situation by the paradoxical behavior of the paralyzed hemidiaphragm during cough when the patient is in the recumbent position. (1) Most patients with recent thoracoplasty necessarily spend considerable time in this position. Any impairment of the mechanism of drainage of bacilli-laden secretions might be expected to increase the incidence of postoperative spread of

<sup>4</sup> On stereoscopic or flat chest roentgenograms

<sup>5</sup> Three or more negative 50 hour concentrated smears in most cases

<sup>6</sup> See first footnote, table 3

disease. While observations in the immediate postoperative period (table 2) failed to confirm this hypothesis, the group with normal diaphragmatic function seemed to handle "spreads" somewhat better, at least from the standpoint of late results (table 3).

Another theoretical objection to thoracoplasty in the absence of homolateral hemidiaphragmatic ventilatory function is the possible creation of a shunt, with the pulmonary vessels circulating blood through lung tissue which can no longer

TABLE 3

*Relation of Late Results after Thoracoplasty to the Preoperative Condition of the Homolateral Hemidiaphragm in 103 Cases, 1929-1944*

	PARTIAL OR TOTAL PARALYSIS			NO PARALYSIS
	Became Permanent	Temporary or Presumably Temporary	Total	
Total Cases 103	19	22	41	62
Satisfactory				
Prompt recovery	10	10	20	35
Delayed recovery	<u>1</u>	<u>1</u>	<u>2</u>	<u>8</u>
Total	11 (58 ± 0%)	11 (55 ± 5%)	22 (56 ± 1%)	43 (73 ± 2%)
Poor				
Operative deaths	2	1	3	4
Death from progressive tuberculosis 6 months to 3 years later	2	4	6	2
Became chronic invalid	3	3	6	7
Recovery, with significant relapse within 3 years*	<u>1</u>	<u>1</u>	<u>2</u>	<u>3</u>
Total	8 (42%)	9 (45%)	17 (44%)	16 (27%)
Nonevaluated Cases				
Nontuberculous deaths 1	0	0	0	1
Contact lost† 4	0	2	2	2

\* In addition to these 5 relapses occurring within the first three years, only 6 late relapses occurred among the 65 satisfactory results in the ensuing 2 to 16 years of additional postthoracoplasty follow-up. Seven of the 11 patients who relapsed have again become arrested.

† All other cases were followed to 1947 or death.

be properly ventilated after the added ventilatory impairment of resection of segments of five or six ribs. Unsaturated arterial blood has actually been obtained under such circumstances in a few instances (9, 10).

#### SUMMARY AND CONCLUSIONS

1. Late results with thoracoplasty in a series of 103 patients were less favorable when the homolateral hemidiaphragm was partially or totally disabled at the time of operation.

2 The frequency of spread of disease after thoracoplasty stages was not altered by disability of the homolateral hemidiaphragm at the time of operation

3 The incidence of general atelectasis of the homolateral lung after one thoracoplasty stage was 10 per cent in patients with a simultaneously disabled homolateral hemidiaphragm and 12 per cent in patients with a normal diaphragm

#### SUMARIO Y CONCLUSIONES

#### *La Interrupción del Frénico en el Tratamiento de la Tuberculosis Pulmonar III Efecto de una Parálisis Hemidiafragmática sobre el Resultado de la Toracoplastia Homolateral*

1 Los resultados tardíos de la toracoplastia en una serie de 103 enfermos fueron menos favorables cuando el hemidiafragma homolateral se hallaba parcial o totalmente incapacitado en el momento de la operación

2 La incapacitación del hemidiafragma homolateral no alteró la frecuencia de la difusión de la enfermedad después de los distintos tiempos de la toracoplastia

3 La incidencia de atelectasia general del pulmón homolateral después de un tiempo de la toracoplastia representó 10 por ciento en los enfermos con un hemidiafragma homolateral incapacitado simultáneamente y 12 por ciento en los que tenían diafragmas normales

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# PHYSICAL THERAPY IN POSTTHORACOPLASTY<sup>1 2</sup>

## One Year's Notes and Observations

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### GENERAL CONSIDERATIONS

The relatively recent employment of physical therapy in postthoracoplasty work has prompted us to keep careful records and to recount our notes and observations in this report, in order to supplement in detail the excellent articles (5, 6, 7, 10) already published on the subject.

The work was carried out in a 619 bed Veterans Administration hospital for tuberculous patients.

The purpose of the study was to observe the skeletal and the muscular function changes which result from the thoracoplasty operations and to determine whether these changes can be prevented or minimized to any extent. Towards these ends the patients' chest roentgenograms were studied to note spinal deviations. In addition, photographs were taken preoperatively, between stages, and postoperatively, and postural examinations were made along with the photographs. Muscle function tests were done in a limited way during the physical therapy program in order to compare the muscle function on the operated side with that on the nonoperated side. More complete information about muscle function was gained from those thoracoplasty patients who were on the ambulant ward and whose work tolerance permitted more detailed examination.

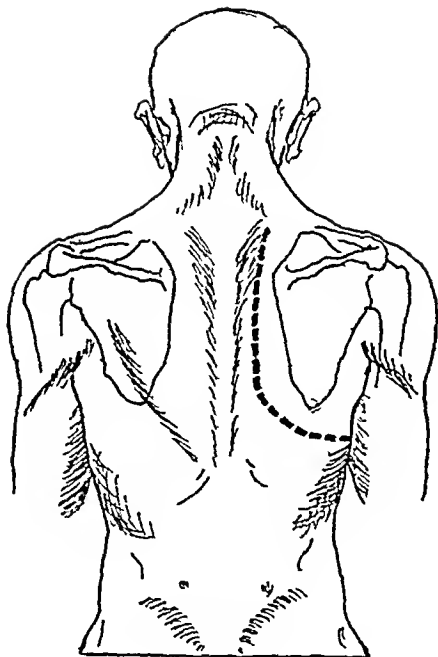
During the year October 1946 to October 1947, 60 patients were seen. Of this number 21 patients had already undergone surgery when the present program of physical therapy was started in October 1946. These 21 patients ranged from one who had the first surgical stage fourteen months previously to those who were still undergoing further surgery. Included in the total were 7 patients who had surgery at other Veterans Administration hospitals and who came to this hospital for convalescent care. While we are not entirely familiar with the physical therapy given those who were not under our care from the start, the photographs taken and the chest roentgenograms of these patients studied did help us to find out, without considering their previous physical therapy, what changes may result from thoracoplastic operations.

The patients were all males ranging in age at the time of surgery from 21 to 53, with an average age of 33. Slightly more than 50 per cent were in the 20 to 29 age group.

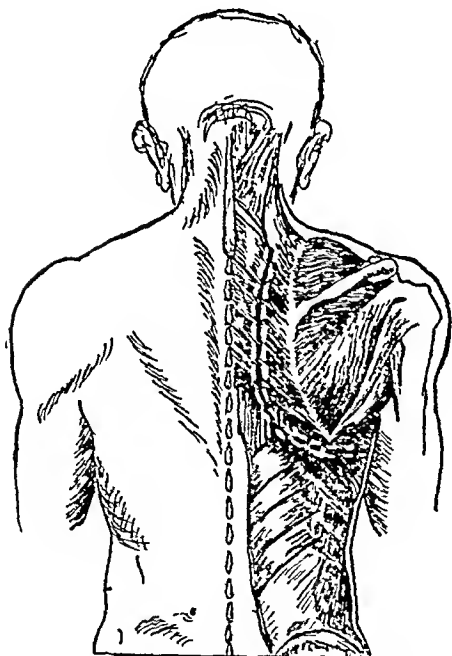
<sup>1</sup> From the Physical Medicine Rehabilitation Service, Veterans Administration Hospital, Castle Point, New York.

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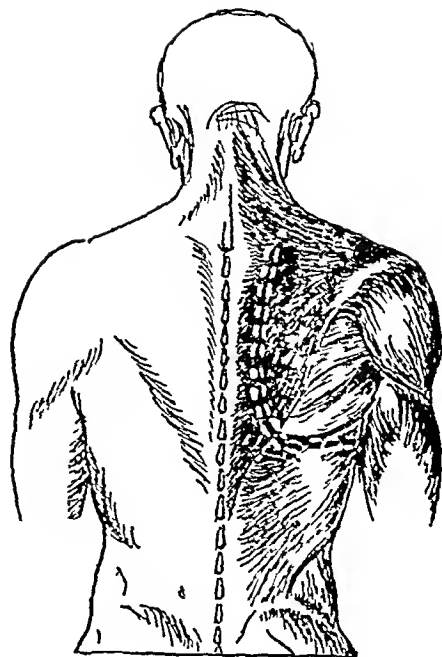
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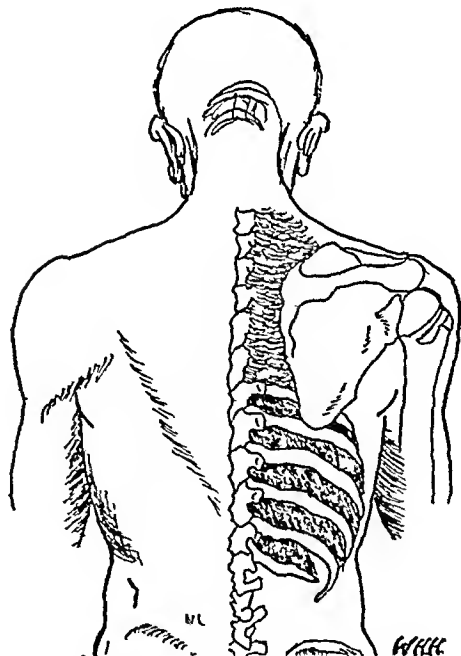


FIG 1 The skin incision starts at the base of the neck between the spinal column and the scapula, proceeds downward and curves under the inferior angle of the scapula at about the level of the eighth rib, and terminates at the mid-axillary line

FIG 2 The incision through the first layer of muscles cuts through the trapezius and the latissimus dorsi

FIG 3 Through the second layer of muscles the incision traverses the rhomboideus minor and major and the lower digitations of the serratus anterior near its insertion

FIG 4 Shows the defect resulting from the removal of several ribs including the transverse processes to which they are attached. The overlying and adjacent structures have been omitted for convenience of illustration. Actually the periosteum and its muscular attachments remain on the chest wall. The erector spinae muscles are retracted medially during the operation and portions of this muscle group are separated from the parts resected

Photographs, notes, and observations made on the original 60 patients subsequent to October 1917 and up to the final draft of this article will be included

### THE THORACOPLASTY PROCEDURE

A brief description of a thoracoplasty operation follows to acquaint the readers with the structures involved and the postoperative physical therapy problems encountered

A thoracoplasty consists of a subperiosteal resection of ribs for the purposes of permanently collapsing the chest wall in order to relax the lung or to obliterate an empyema space. Surgery is performed in one to four stages, depending on the site of the cavity. If the cavity in the lung is in the apex, only one or two stages may be necessary. Lesions situated lower in the lung may require up to four stages and the resection of ten ribs. The usual surgical procedure at this hospital involved a seven rib resection done in three stages. The first three ribs are resected during the first stage. Ribs 1 and 5 are removed during the second stage, and the next two ribs are taken at the third stage. Multiple stages, or operations, are done to lessen the effects of surgical shock and paradoxical respiration, and thereby to reduce the operative risk.

It should be noted that nothing is done to the affected lung itself. By removing the supporting rib structure the chest wall collapses and the underlying lung is permitted to relax and conform to the newly contoured chest wall. Compression by the shoulder girdle and scapula also plays a part in delineating the new contour of the chest wall.

The thoracoplasty procedure (figures 1, 2, 3, 4) consists essentially of an incision starting at the base of the neck, between the spinal column and the vertebral border of the scapula, and proceeds downward between these structures, curving outwardly under the inferior angle of the scapula and terminating at the mid-axillary line (figure 1). The first layer of muscles incised are the trapezius and the latissimus dorsi (figure 2). The second muscular layer consists of the rhomboideus minor and major and the digitations of the serratus anterior (figure 3). Then the vertebral border of the scapula is lifted and the origins of the serratus anterior muscle are separated from the upper five or six ribs. This permits the scapula to be retracted laterally. The erector spinae muscles are retracted medially and a subperiosteal rib resection is done, including the transverse processes. The periosteum and the muscles separated from the resected structures remain on the chest wall. Bone regeneration starts from the periosteum, forming a firm, newly-contoured chest wall and maintaining the lung in a permanently collapsed position. The entire process of rib regeneration requires about four months.

Figure 4 shows a chest from which several ribs and vertebral transverse processes have been removed. The muscular structures have been omitted for convenience of illustration. The muscles which are separated from the resected skeletal structures soon reattach themselves to the adjacent tissues.

Some of the affected muscles about whose functions we are concerned are the trapezius, latissimus dorsi, rhomboides, serratus anterior, pectoralis major, erector spinae, and the scaleni group.

The stages of surgery are usually performed two to three weeks apart, gaining entrance into the operative field by excision of the previous incision scar. It should be noted here that the same muscle layers are incised at each stage.

### PHYSICAL THERAPY

The physical therapy program as given here represents a compromise between rest and exercise. Most of the patients undergoing a thoracoplasty have active symptoms of tuberculosis and for them the desired regimen is rest. There are some undesirable postoperative sequelae, however, such as skeletal deviations

and muscular and joint dysfunction of the shoulder girdle on the operated side. The physical therapy program entails the minimum specifically localized activity which will accomplish the desired results. These are an active full range of shoulder girdle movements, maintenance of muscle tone in the surgical area, and the preservation of a symmetrical bodily alignment.

Linduff (7) recently described the physical therapy procedures for chest surgery conditions, among them thoracoplasty. Our methods follow closely those of Linduff, being somewhat modified to meet the requirements of the staff surgeons. Whenever a question has arisen as to any particular activity being too strenuous, the choice has always been in favor of less activity.

Briefly, the following is an outline of the physical procedures used in post-thoracoplasty.

#### *Preoperative*

- 1 A preoperative photograph, posterior view, is taken as a basis for comparison with the postoperative photo.
- 2 The patient is made acquainted with the postoperative problems.
  - (a) pain and soreness of the affected muscles, interfering temporarily with the shoulder girdle movements
  - (b) the possible skeletal deviations which may result from surgery are mentioned and the patient is told how to guard against them
- 3 The patient is shown the specific local exercises he will do postoperatively and he performs them as demonstrated by the physical therapist.
  - (a) glenohumeral and shoulder girdle movements
  - (b) diaphragmatic breathing
  - (c) mild abdominal exercise consisting mostly of pelvic tilting for postural correction
- 4 Correct bodily alignment in bed is stressed.
  - (a) head and neck straight, especially after the first stage of surgery when the head and neck tend to deviate laterally towards the nonoperated side
  - (b) shoulders level, the tendency being for the shoulder girdle to elevate on the operated side
  - (c) the main body masses, head, thorax, and pelvis should be maintained in a straight line

#### *Postoperative*

- 1 The body alignment is checked in bed as soon as the patient is free from the effects of the anesthetic. Caution is exercised so as not to interfere with nursing care.
- 2 Diaphragmatic breathing is started early to encourage relaxed breathing. Chest expansion is avoided so as to facilitate pulmonary collapse.
- 3 Active assistive exercises are given consisting of
  - (a) the normal glenohumeral movements
  - (b) horizontal abduction and adduction of the humerus
  - (c) abduction and adduction of the scapula
  - (d) depression of the shoulder girdle
  - (e) combined movements of adduction of the scapula and hyperextension of the humerus

The movements of adduction of the scapula, alone and combined with hyperextension of the humerus, are done in the prone-lying position when the patient is able to turn over. All other movements are carried out in the supine-lying position.

*Procedure*

The exercises are usually started with the staff surgeon's approval, on the third postoperative day. The patient is first made comfortable in the supine-lying position by placing a pillow under the knees and, if necessary, one under the head. Each movement is performed by the patient as far as he is able and then is assisted to the point within the tolerance of pain. Each movement is done twice at first. Lindahl (7) suggests that at the end of the seventh day each exercise may be performed five times, twice a day. Since the emphasis at our institution is on minimum activity, the maximum for each exercise is three times, once a day. It is most essential that all movements be done slowly with adequate rest periods intervening.

*Precautions*

1. A temperature of 100°F. or over contraindicates treatment.
2. If the pulse rate does not return to the pre-exercise level within five minutes after exercise, the amount of activity given the next day is reduced. Usually, even when the pulse is rather high to start with, if the exercises are given slowly with adequate rest periods between movements, the pulse will remain fairly stable. An unusually rapid pulse for a given patient contraindicates treatment.
3. Hemoptysis is a definite contraindication for treatment.
4. Other limiting factors to the exercise routine are cardiac disturbances in the older patients, or a spread of the disease in the same or into the contralateral lung, and such other indications as the thoracic surgeon in charge of the case may deem significant.

## POSTTHORACOPLASTY CHANGES

The possible postthoracoplasty changes may be divided into two categories: scoliosis with its concomitant skeletal changes, and skeletal deviations of the shoulder girdle and changes in muscle function as related to the surgical trauma.

*Scoliosis and Concomitant Skeletal Changes*

Scoliosis, in general, may be caused by any one of several conditions, among them thoracoplasty. Regardless of the cause, the mechanism for the development of scoliosis is the same. We shall consider first the general characteristics of scoliosis and then relate these characteristics to postthoracoplasty findings.

Lovett (8) described the movements of the spinal column as four in number: flexion, extension, lateral flexion, and rotation. Considering only the dorsal and lumbar segments for the moment, flexion and extension of the spine are essentially movements of the lower two dorsal and the lumbar vertebrae. Lateral flexion is also most free in this area. Rotation is primarily a movement of the dorsal spine. Actually, lateral flexion and rotation are two elements of a compound movement, one usually accompanies the other.

Lovett (8) explains the reason for the two movements, lateral flexion and rotation, acting together on the basis of the mechanical law that governs flexible rods. When an attempt is made to bend a flexible rod in two planes at the same time, a twisting or rotation of the rod will result. In the case of the spinal column,



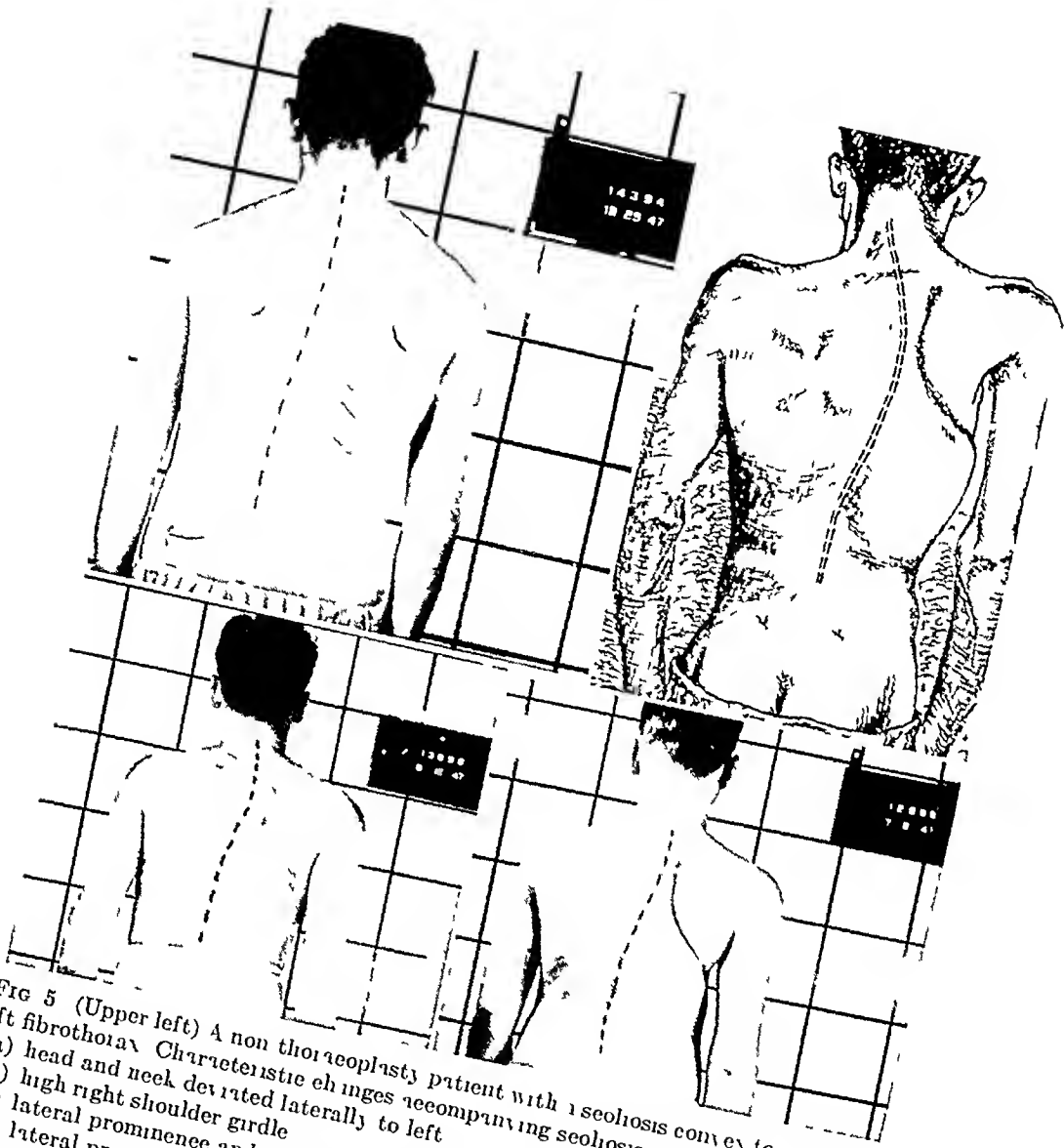


FIG 5 (Upper left) A non thoracoplasty patient with a scoliosis convex to right, due to a left fibrothorax. Characteristic changes accompanying scoliosis are present  
 (a) head and neck deviated laterally to left  
 (b) high right shoulder girdle  
 (c) lateral prominence and posterior rotation of right thorax  
 (d) lateral prominence and anterior rotation of left pelvis

FIG 6 (Upper right) Possible skeletal changes resulting from thoracoplasty  
 (a) deviation of head and neck towards the nonoperated side  
 (b) elevated and anteriorly displaced shoulder girdle on the operated side  
 (c) lateral curvature of the cervical dorsal spine convex towards the operated side  
 (d) lateral prominence of the thorax on the operated side, often associated with rotation posteriorly  
 (e) lateral prominence, often combined with anterior rotation, of the pelvis on the contralateral side

FIG 7 (Lower left) A 27 year old patient with a 3 stage, 7 rib resection. Patient is of muscular build and quite proud of personal appearance

FIG 8 (Lower right) A 25 year old patient with a 4 stage, 8 rib resection (Fourth stage included a revision and resection of the eighth rib). Head and neck are straight and the shoulders level, with the lateral curvature fairly well compensated and the body symmetrically aligned

which may be considered a flexible rod, it is normally bent or curved in the antero-posterior plane. If a bend in the lateral plane is imposed upon it, it will cause the spine to twist on itself and the twisting will take place most markedly in the area which permits the freest rotatory movement, the dorsal spine. When, for any reason, the spine habitually assumes this position of bending in two planes at the same time, certain structural changes take place, the most pronounced being a lateral curvature of the spine with vertebral rotation towards the convexity of the curve.

Accompanying the lateral curvature of the spine are certain characteristic skeletal changes. The rotation of the vertebral bodies towards the convexity of the lateral curve carries with it the thoracic cage, causing it to bulge laterally and posteriorly. The shoulder girdle on the convex side of the curve will usually be elevated and the head and upper cervical spine will tend to counterbalance by tilting slightly towards the high shoulder girdle. Compensatory changes are often evident lower in the spinal column, characterized by a laterally prominent and anteriorly rotated pelvis on the side contralateral to the prominent thorax (figure 5). These are the most prominent skeletal changes associated with scoliosis and they are to a variable degree what is seen in postthoracoplasty patients.

The direct cause for the scoliosis resulting from thoracoplasty is a mechanical imbalance created by the traumatization and weakening of the trunk muscles on the operated side and by the rib resection. In a seven rib resection, with the transverse processes removed, a number of muscles lose their points of origin, some their insertions, and others both their origins and insertions. Among the latter group of muscles are the intercostals which ordinarily exert a balancing force on the rib cage and indirectly on the spinal column. The net result is a lateral bending of the spine towards the stronger, nonoperated side.

Scoliosis was a common finding in all our thoracoplasty patients, as seen on the chest roentgenograms and on the photographs with spinal markings. Not always was the scoliosis evident to the eye from examination alone. Some patients, except for the scar, showed little outward manifestations of the thoracoplasty. In these cases the scoliosis was of slight degree and the outer integument covered over quite well the underlying skeletal structure, giving the appearance of a symmetrical body. Most of the patients, however, showed varying degrees of skeletal deviations, depending upon the severity of the scoliosis.

The first sign of scoliosis, as observed on the chest roentgenograms, is evident after the first stage of surgery in the cervical and upper dorsal region. The lateral curvature resulting from thoracoplasty is always convex to the operated side (figure 6).

After the first stage there may be a noticeable elevation of the shoulder girdle on the operated side with the arm adducted closely to the thorax. An elevated shoulder girdle on the convex side of a scoliosis is quite common. It may be exaggerated because of the pressure and bulk of the compression chest bandage. The upper trapezius, pectoralis major, and latissimus dorsi are often contracted, probably a reflex attempt on the part of the body to splint and protect the operated area. Parts of these muscles are also involved in the surgical procedure which is undoubtedly a cause for their increased tension.

As the stages of surgery progress, there is often a noticeable increase in the lateral curve in the cervical and dorsal regions, as noted on the chest roentgenograms. On clinical examination the remaining ribs on the operated side will often show greater angulation laterally and they may also be rotated posteriorly, depending upon the severity of the scoliosis. The pelvis on the contralateral side is prominent laterally and may show a rotation anteriorly, the latter indicating a compensatory lumbar curve (9, 11).

Viewed posteriorly in the standing position, the head and cervical region deviate towards the nonoperated side and the trunk and shoulders appear to be displaced laterally towards the operated side, at an oblique angle (figure 6).

With or without the benefit of physical therapy, the scoliotic changes seem to take place within a short time, starting soon after the first stage and are virtually completed shortly after the last stage. To what extent physical therapy can minimize the scoliosis has not as yet been determined. However, the scoliosis is not a progressive condition. Chest roentgenograms taken soon after the last stage compared with those taken a year later show no appreciable change in the spinal deviation.

The chest roentgenograms available to us showed only the lower cervical and entire thoracic spine. From these films it was noted that the apex of the lateral deviation was usually somewhere in the area of the fourth to sixth dorsal vertebrae. There was undoubtedly a compensatory curve lower in the spine in many of our patients, as evidenced by external pelvic alterations.

### *Shoulder Girdle Changes*

*Skeletal* It has already been noted that accompanying scoliosis there is usually a slight elevation of the shoulder girdle on the operated side. The elevation may be temporarily increased by the compression bandage and by contracted muscles reflexly splinting the operated field. The shoulder girdle may also be forced into a high position by a "hanging up," as the patients express it, of the scapula on the uppermost intact rib. This may occur after the removal of five to seven ribs and is common after the second stage, less common after the third. The uppermost unresected rib forms a shelf structure and the inferior angle of the scapula comes to rest upon the intercostal muscles which are in intimate contact with the shelf. The scapula at rest or during movement may cause mechanical irritation and pain, and the patient may elevate the girdle still higher to prevent the irritation. This phenomenon is often transitory in nature, subsiding after the next stage of surgery. When no more stages are contemplated and the irritation persists, a partial scapulectomy may be done in which the distal half of the scapula is excised. The present practice is to do the partial scapulectomy with the last stage when it appears that the inferior angle will be a hindrance to comfort and shoulder girdle functioning.

Occasionally the shoulder girdle persists in its elevated position even after the underlying cause is relieved. Alexander (1) attributes this to "organization of fibrous tissue in the field of operation beneath the scapula."

With an elevated shoulder girdle one usually finds a deepening of the supraclavicular fossa.

Another common finding is an anterior displacement of the shoulder girdle on the operated side (figure 10). The depression of the chest wall, observable anteriorly and posteriorly (figures 11, 16), created by the resection of ribs, permits the scapula to move forward into the decostalized area, carrying with it the clavicle and humerus. This forward displacement seems to place the scapular muscles at a mechanical disadvantage in certain of their movements, especially adduction.

Some degree of shoulder girdle elevation on the operated side was evident in many of our patients. The anterior displacement of the girdle, when noted, was



FIGS. 9, 10, 11. A 41-year-old patient, who had a 2-stage, 7-rib resection at another institution, presents several interesting points.

FIG. 9 (Left) Shows a mild, well-compensated lateral curvature with a slightly elevated right shoulder girdle. Patient's history revealed a preoperative spinal curvature convex to left in dorsal region, and a postoperative wound infection after second stage, necessitating strapping of arm to side for about six weeks. When patient reported for convalescent care he displayed tightness of pectoralis major and latissimus dorsi on right, with limitation of glenohumeral joint in flexion, abduction, and external rotation. Patient also complained of pain in region of right inferior angle of scapula, which was probably mechanical irritation between the latter and the eighth rib and possibly the cause for the elevated shoulder girdle on right side. The preoperative curvature convex to left now appears as a mild right cervical dorsal, left dorsal-lumbar curve.

FIG. 10 (Center) A lateral view of same patient showing forward displacement of shoulder girdle on operated side.

FIG. 11 (Right) Anterior view of same patient showing depression in right infraclavicular region due to resection of ribs, and a deepening of the supraclavicular fossa.

little influenced by the exercise program and seemed more a natural consequence of the surgical procedure.

*Muscle function changes.* After each stage the movements of the humerus away from the body are somewhat limited beyond a right angle. The contracted adductors, the pectoralis major and latissimus dorsi, limit the range of movement. As treatment continues, greater range is gradually attained.

A phenomenon frequently observed in those who had had three or more incisions through the trapezius, was a noticeable movement of the scapula upward and away from the body when the arm was abducted (figure 14). The superior angle of the scapula would rise above the outline of the shoulder and the vertebral border move somewhat posteriorly away from the chest wall. This is similar, but

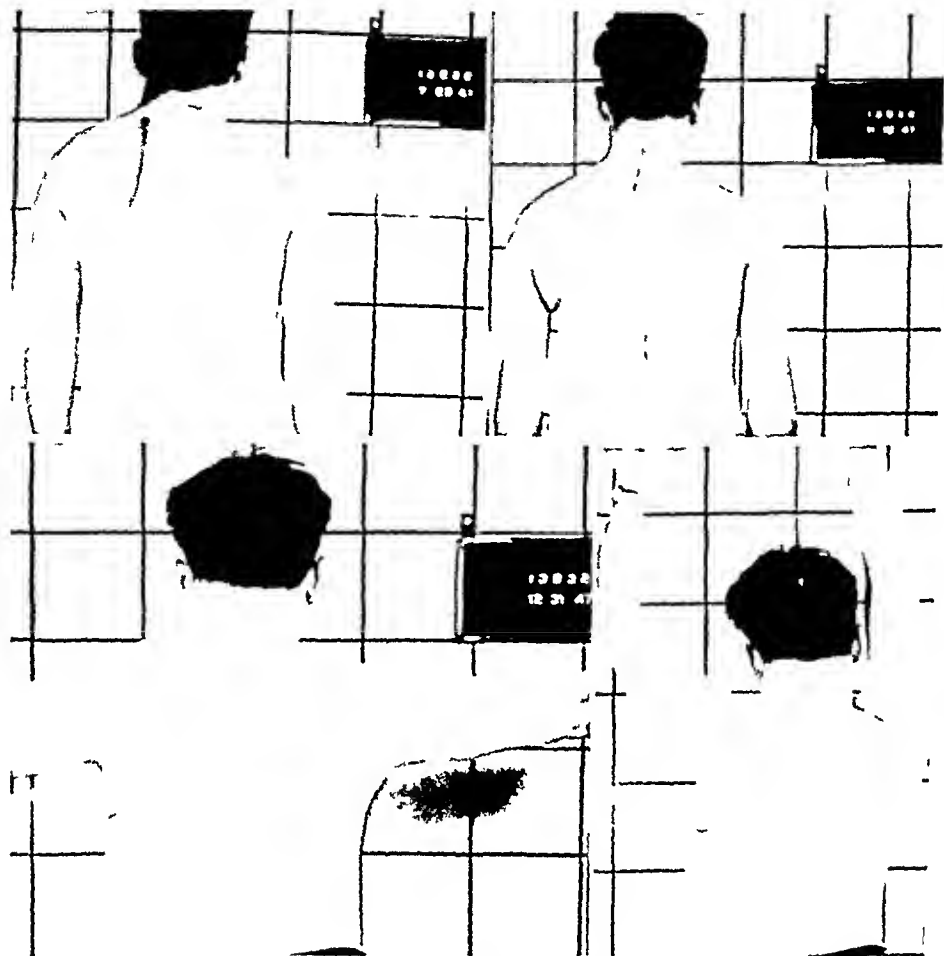


FIG 12 (Upper left) A 24 year old patient with a 2nd stage, 5 rib resection. The left shoulder girdle is quite noticeably elevated, almost obliterating the normal neck contour. Inability to depress the shoulder girdle is due to the scapula sitting on the shelf formed by the sixth rib. Glenohumeral movements limited to 90 degrees in flexion and abduction.

FIG 13 (Upper right) Same patient as in figure 12, four weeks after a partial scapulectomy was performed. Left shoulder girdle has returned almost to a level position and the neck lines are greatly improved in appearance. Glenohumeral movements are now freer with some pain persisting in the upper reaches of abduction.

FIG 14 (Lower left) Same patient as in figures 12 and 13, with arms abducted to a right angle. Note elevated superior angle of scapula and posterior protrusion of vertebral border of scapula, left, indicating weakened trapezius.

FIG 15 (Lower right) Same patient as in figure 14, with arms abducted beyond right angle. Arm on operated side has moved towards flexion and is limited about 40 degrees short of full abduction. Arm can be moved passively to full range.

to a lesser degree, to what Wright (12) noted in a case of paralysis of the trapezius muscle. In the case of the thoracoplasty patient, it represents a weakened trapezius. The movement of flexion of the glenohumeral joint elicits the same reaction of the scapula. As the movement of abduction continues beyond a right

angle, in these patients, the arm tends to move in the direction of flexion, and active abduction may be limited twenty to thirty degrees, and sometimes more (figure 15). Passively the arm can usually be moved to the completion of full range. The serratus anterior may share to some extent in the disturbed functioning of this movement since it acts on the scapula in conjunction with the trapezius. One of our surgeons has noted that the trapezius frequently is adherent to the scar of the deeper muscles and of the subcutaneous incision. It is his opinion that this may be a cause for the disturbed functioning of the trapezius.

In spite of the limitation of shoulder movements in the upper ranges, when they are tested routinely several months after the last stage of surgery, they display good or normal strength as compared with the nonoperated glenohumeral joint.

The rhomboideus minor and major muscles often show up their weakness in those movements in which they participate, especially when the movements are resisted. Normally one of the functions of the rhomboidei, together with the lower fibers of the trapezius, is as a stabilizer of the scapula in adduction or extension of the humerus. As a result of surgical incision during each stage the stabilizing action is impaired and the corresponding glenohumeral movements are weak and unsteady. Moreover, adduction of the scapula, a prime movement of the rhomboidei, is similarly involved.

Commonly associated with an elevated shoulder girdle are contracted upper fibers of the trapezius.

Patients often complain of a sharp pain or a persistently dull pain, aggravated by certain shoulder movements. The site of pain may be in the area of the shoulder joint, or along the medial or lateral aspect of the arm, or intercostally, or at the line of incision. Pain may be directly attributable to the section of some small nerves during surgery and it persists for variable lengths of time.

#### *Factors Related to the Degree of Scoliosis and Concomitant Skeletal Deviations*

From the start we have been particularly impressed by the difference between our patients in their external physical appearance after having been subjected to surgery. The question arises, "Why is the cosmetic result better in one patient than it is in another?" Rather briefly and inconclusively we shall consider those factors which in our opinion seem pertinent.

*Exercise program.* The exercise program has three main purposes: (a) maintenance of full range of active motion of the shoulder girdle on the operated side, (b) maintenance of muscle tone in the surgical area, (c) preservation of a symmetrical bodily alignment.

Barring complications which limit physical activity, such as wound infection, cardiac dysfunctioning, or spread of the disease, the exercise program will usually accomplish the first two objectives. At least the two objectives will be attained to the point that a degree of useful functioning sufficient for every day purposes will be present. Concerning the third objective, the preservation of a symmetrical bodily alignment, there are probably other factors which affect the end result, and these factors will be taken up in turn. But we must assume in all cases that

the objectives can be attained if we are to obtain the maximum results from physical therapy. The minimization of the skeletal deviations, by instruction in proper bed positioning, is more effective than the later attempt at correction. It is estimated that it requires about three weeks for the detached muscles to re-attach themselves, and about four months for the ribs to regenerate. During this time, which means between stages and for about four months following the last stage, the patient needs to be constantly reminded and assisted in keeping the body in good alignment. And the same is true when the patient becomes ambulant.

*Age* At first it seemed that the younger patients, particularly those under 25 years of age, developed a greater degree of scoliosis than the older patients. But this was found not to be true. Our youngest patients were 21 years old. At another institution we visited, where there were patients younger than 21, it was the opinion of the staff physicians that the scoliosis was greater in this younger age group, although older patients may and do develop the condition to a similar degree.

Cleveland (2) studied a series of 6 children with thoracoplasty and compared them to a typical adult thoracoplasty patient. The children (average age 14 years) developed a lateral curvature of 25 to 30 degrees one year postoperatively, and the adult, age 25, showed a curvature of 13 degrees at nine months postoperatively. The adult displayed about the same degree of spinal deviation at two weeks postoperatively as at nine months, while the curvature of the children tended to increase up to nine months to a year postoperatively and then remained stable. One striking exception occurred in a 12 year old patient who progressed to a 73 degree dorsal curve over a period of twenty-one months. The author states that "the amount of deformity to be expected will vary directly with the potential growth remaining in the spine."

Alexander (1) perhaps furnished an additional clue when he stated, "the anatomical changes tend to be greater in young persons with elastic chests and undeveloped muscles than in well-developed adults whose chests are relatively rigid and stable. Poorly developed adults react much as children do."

*Nature of Surgery* It can be stated with reasonable safety that a one stage thoracoplasty will show less skeletal defect than a thoracoplasty of two or more stages. The more ribs resected, together with the removal of the transverse processes, usually makes for a greater lateral curvature.

Seven ribs may be resected in two or three stages. The number of stages will influence the strength of the musculature involved, especially those muscles which are incised at each stage.

The excision of the vertebral transverse processes makes for a better collapse of the lung, but at the same time it seems to increase the scoliosis. At two other institutions we have noted that the transverse processes are not disturbed, or are only partially removed, with apparent lessening in the degree of scoliosis. The small intertransverse muscles and ligaments and the muscles of the deep layer of the back which are attached to the transverse processes probably exert an important stabilizing effect on the spine.

Recently the surgical approach has been modified in selected cases. The technique is referred to as a muscle split thoracoplasty. It is used on those patients who have a cavity high in the apex of the lung and who do not require the resection of more than five ribs. The first stage incision is performed on a line parallel to the fibers of the mid-trapezius and the rhomboid (figure 23). These

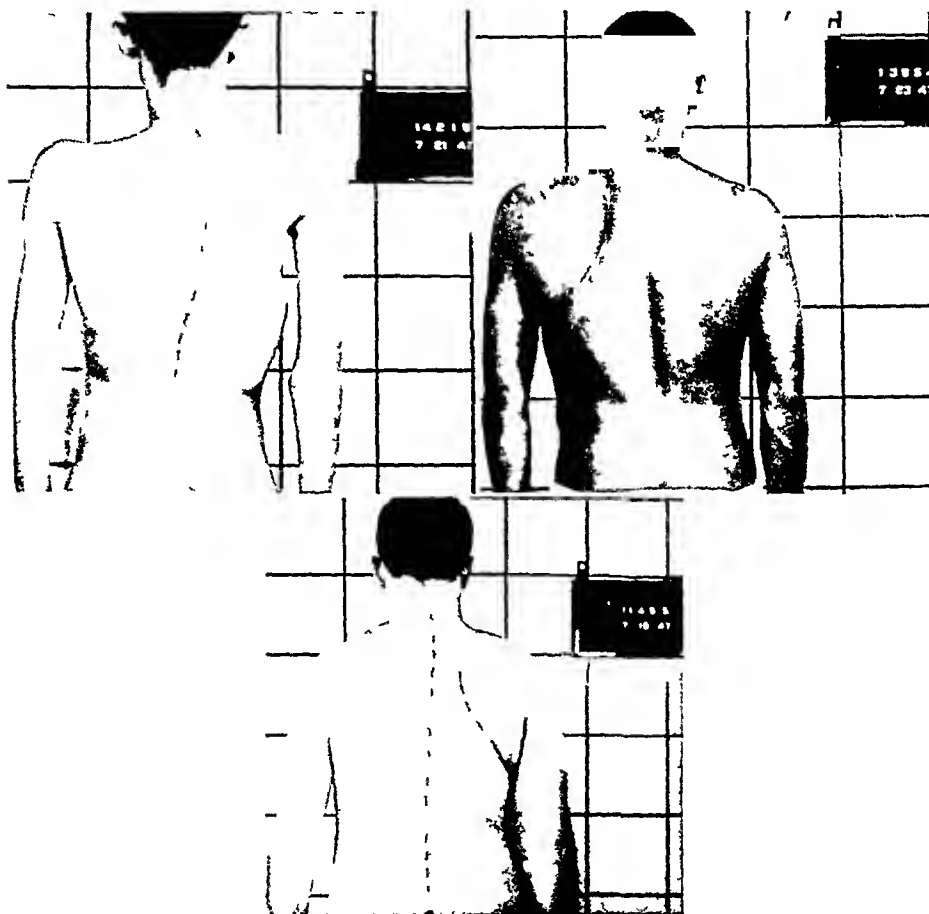


FIG 16 (Upper left) A 28 year old patient with 3 stages, 7 ribs resected. A long, thin body often accentuates the existing deviations. Photograph illustrates depression of upper chest wall posteriorly.

FIG 17 (Upper right) A 46 year old patient who has had 3 stages, 7 ribs resected. The heavier, muscular patients often cover over well the existing skeletal deviations.

FIG 18 (Lower) A 28 year old patient who went through 2 stages, 5 ribs resected, and also a partial scapulectomy. This illustrates a heavy set, symmetrically aligned patient.

muscle fibers are separated, rather than cut transversely, and the posterior sections of the upper five ribs are removed. The second stage incision is done along the mid-axillary line (figure 24) and the anterior segments of the first five ribs are resected. This procedure is less traumatizing and less destructive to the musculature of the shoulder girdle usually involved in a thoracoplasty. It makes for



a better functional end result. What effect it has on the scoliosis has not as yet been determined. The patients on whom this procedure has been used are not included in the original 60 patients we have studied.

*Condition of spine prior to surgery* Among our patients were a few who, previous to surgery, had developed a fibrothorax, and the thorax was contracted towards the same side. This pulling over of the trunk, maintained over a period of time, caused a scoliosis convex to the opposite side (figures 5, 19). It has already been noted that the thoracoplasty brings with it a lateral curvature convex towards the operated, affected side. When the two processes are combined, the fibrotic scoliosis and the thoracoplasty scoliosis, the result is a mild, compensated curve, convex to the operated side in the cervical-dorsal region and convex to the opposite side in the dorsolumbar regions (figures 9, 20). The thoracoplasty tends

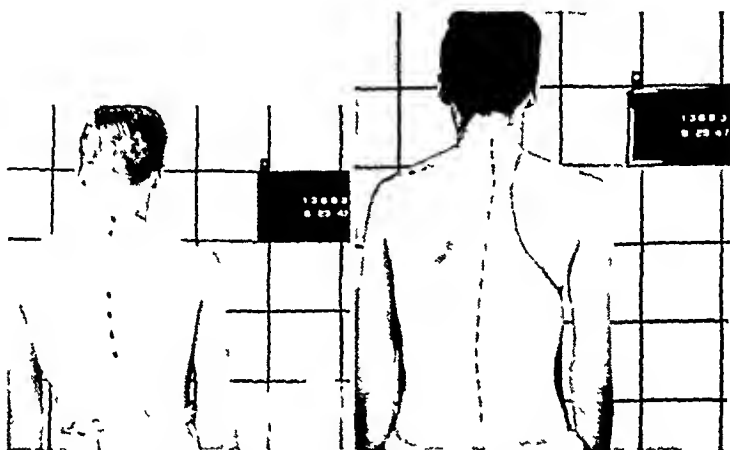


FIG 19 (Left) Preoperative photograph of a 26 year old patient showing a curvature of spine, convex to left. Right fibrothorax has caused the trunk to bend laterally to the right.

FIG 20 (Right) Same patient as in figure 19, after a 3 stage, 7 rib resection. The lateral curvature of the spine has changed to a mild right cervical dorsal, left dorsal-lumbar curve, and the patient is fairly well aligned.

to counteract the fibrotic contracture, minimizing the lateral curvature. The same is true in cases of empyema.

*Morphological type* We have already quoted Alexander's statement to the effect that adults with poorly developed muscles tend to show greater anatomical changes than do well-developed individuals. In general, we have noted that the thin, asthenic individual shows up poorer than the stocky or heavy set, muscular one. While there may not always be a greater degree of scoliosis and accompanying changes in the thin patient, there is quite often an accentuation of the existing deviations (figures 16, 21). The thin patient's bodily contours are more sharply defined, whereas the heavy set patient fills in and covers over the hollows and prominences created by surgery (figures 17, 18).

*Personality* It would be altogether too easy to say that one patient attained better results because he was more cooperative than one who did not come out too well, but there did seem to be some relationship, in a few patients, between

the personal factor, expressed in terms of personal pride in carriage and bearing, and a good outward appearance (figures 7, 8) Conversely, there were several patients who expressed interest only in getting rid of their tuberculosis and did not particularly care how they looked after surgery, these did not show up too

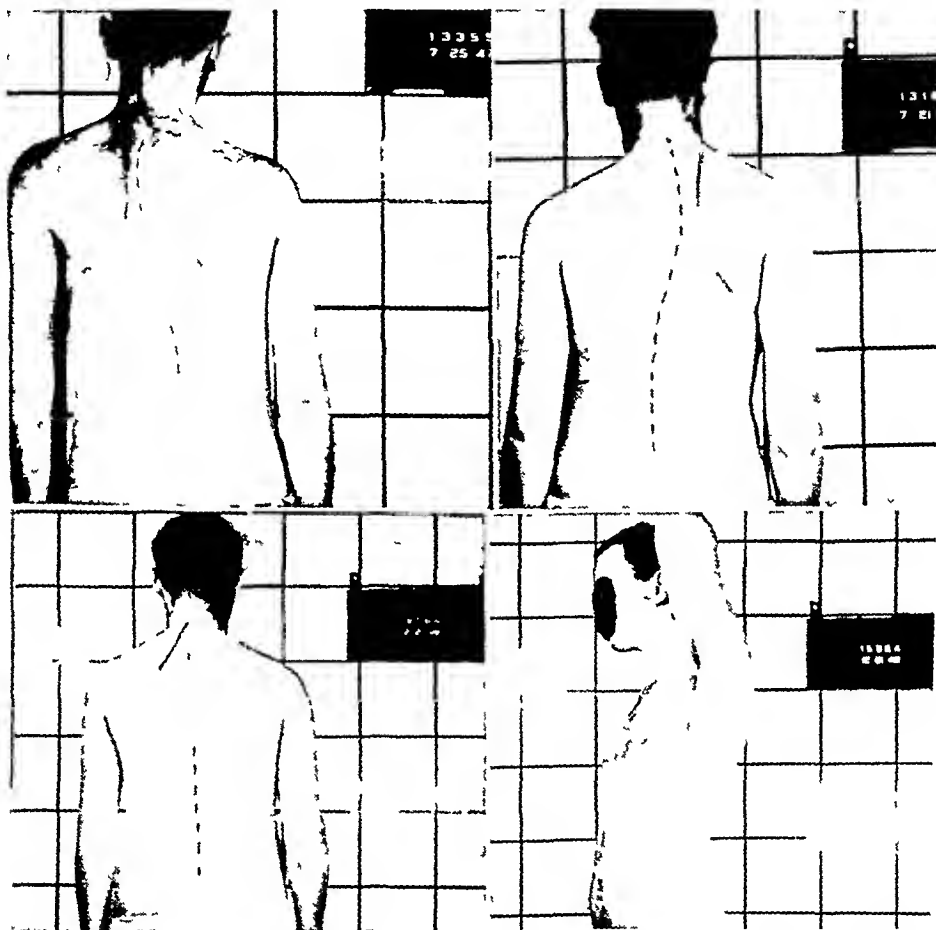


FIG 21 (Upper left) A 29 year old patient who received a 3 stage, 7 rib resection. Of asthenic build, this patient did not care too much about appearance.

FIG 22 (Upper right) A 25 year old patient with a 3 stage, 7 rib resection. Somewhat heavier than the patient in figure 21, this patient was similarly unconcerned about his posture.

FIG 23 (Lower left) Shows first stage incision of a muscle split thoracoplasty. Patient is 27 years old and has had 5 ribs resected in 2 stages.

FIG 24 (Lower right) Same patient as in figure 23, showing the second stage incision of a muscle split thoracoplasty. Incision scars have been darkened in both photographs.

well (figures 21, 22). They just did not bother to exert the effort necessary to maintain good bodily alignment in bed and out of bed, whereas those who took pride in their posture were constantly aware of it and that in itself was sufficient to assure full cooperation.

These statements are based only on those patients from whom we received

some positive pronouncements of active concern or of passive acquiescence, and the number was relatively small in either case. The same process may have been at work in other patients who gave no indication one way or the other.

It is difficult to separate the personal factor, or any one of the factors, from the others which influence the end result of the thoracoplasty.

#### SUMMARY AND CONCLUSION

1 Sixty postthoracoplasty patients were observed during a one year time in a Veterans Hospital for tuberculous patients.

2 The observable changes which resulted from thoracoplasty were classified under two headings:

(a) scoliosis with concomitant skeletal changes of the head and neck, the shoulder girdle on the operated side, the thorax, and the pelvis.

(b) skeletal deviations and changes of muscle function of the shoulder girdle on the operated side.

3 An attempt was made to explain the differences in external appearance resulting from thoracoplasty on the basis of six factors: exercise program, age of patient, nature of surgery, condition of spine prior to surgery, morphological type, and personality.

#### SUMARIO Y CONCLUSIONES

##### *La Fisioterapia en la Posttoracoplastia. Un Año de Notas y Observaciones*

1 Sesenta enfermos posttoracoplásticos fueron observados durante un año en un Hospital de Veteranos para tuberculosos.

2 Las alteraciones observables debidas a la toracoplastia fueron clasificadas bajo dos encabezados: (a) escoliosis con alteraciones esqueléticas concomitantes de la cabeza y la nuca, el anillo del hombro del lado operado, el torax y la pelvis, (b) desviaciones esqueléticas y alteraciones de la función muscular del anillo del hombro del lado operado.

3 Trátase de explicar las diferencias en el aspecto externo debidas a la toracoplastia a base de seis factores: plan de ejercicio, edad del enfermo, naturaleza de la cirugía, estado del raquis antes de la intervención, tipo morfológico, y personalidad.

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# CONCERNING THE LOCATION OF PULMONARY INFARCTION<sup>1</sup>

EUGENE I ZINS<sup>2</sup>

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Despite the voluminous literature available on pulmonary infarction, the site in the lung most often infarcted has been commented upon infrequently. White (1) and others (2, 3) have emphasized that pulmonary infarcts are usually found in the right lung. While this opinion is the most prevalent, there is need for re-evaluation of factual information and reorientation of physiological aspects. Herein lies the purpose of this report. An appraisal of the location of pulmonary

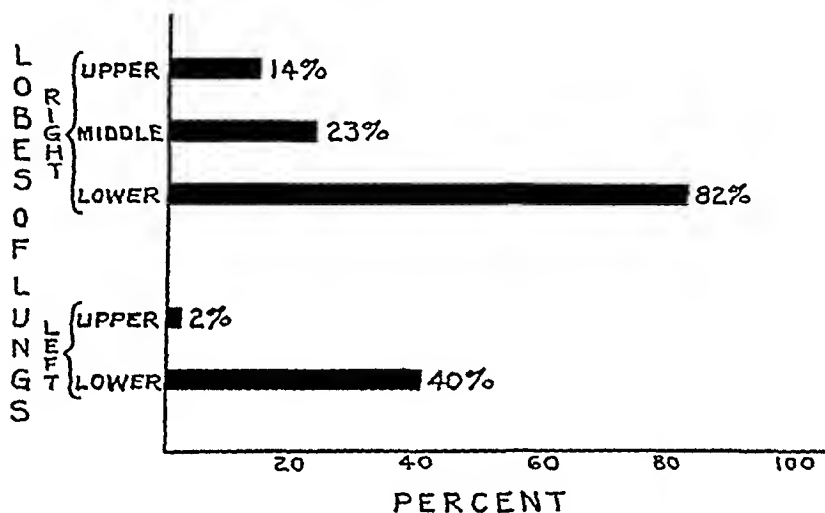


FIG 1 Incidence of specific lobar involvement in 100 cases of pulmonary infarction (multiple involvement in 60 per cent)

infarction should be accompanied by an explanation of the increased frequency of a particular site of involvement.

## OBSERVATIONS

The frequency of involvement of each lobe of the lungs was investigated in 100 cases of pulmonary infarction found at routine necropsy at the Metropolitan Hospital in New York City. Examination of figure 1 reveals that in 82 per cent of the cases the infarct was located in the right lower lobe. The right upper lobes and middle lobes contained relatively few of the infarcts. There were more infarcts in the left lower lobe than in either the right upper or middle lobes. Nevertheless, the number in the left lower lobe was less than one-half that found in the right lower lobe. A total of 119 infarcts were found on the right side while a total of 42 infarcts were present on the left.

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## DISCUSSION

The explanation for the right-sided predominance of pulmonary infarction is presumably related to the presence of congestion. Zahn (4) in 1897 demonstrated that pulmonary infarction was more likely to occur in rabbits after embolization in the presence of passive congestion. Karsner and Ash (5) studied the role of stasis in pulmonary infarction in 1912. In a noteworthy paper it was shown that hemorrhagic infarcts appeared after the ligation of pulmonary arteries when the veins likewise were subjected to ligation. They concluded from the study that simple embolism does not produce pulmonary infarction. Stasis is the necessary corollary and, moreover, the greater the stasis the earlier will infarction occur.

Patients with cardiac disease who are either in acute or chronic failure provide an excellent means for the clinical study of the association of passive congestion and pulmonary infarction. Examination of the protocols of 100 consecutive necropsies of patients with cardiac disease revealed that 33 per cent had demonstrable infarcts. This is in agreement with White (3) and Hinds (6) who state in recent reports that the incidence of pulmonary infarction in cardiac patients is approximately 30 per cent.

The importance of stasis in the genesis of infarction following pulmonary embolism was investigated recently from an experimental standpoint by Moses (7). Pulmonary emboli were produced by inserting into the jugular veins of rabbits wool yarn previously soaked in defibrinated blood. Compression of the thorax, producing congestion, was accomplished with wide rubber bands. A control series of rabbits not subjected to compression of the thorax was likewise studied. In the latter group, bland embolism without infarction was noted at autopsy. When stasis and congestion were produced, hemorrhagic infarcts developed. These observations stressed the importance of preventing circulatory stasis in order to prevent pulmonary infarction.

Evidence of a confirmatory nature is presented by examination of the pulmonary artery for emboli in the absence of infarction and congestion. It has been estimated by Belt (8) that only 50 per cent of emboli cause infarction. In the absence of predisposing factors for infarction, embolization may not produce pathological changes in the lungs.

Thus, congestion has been shown to be a factor of the greatest importance. Study of this alteration of normal physiology affords a possible explanation for the localization of most pulmonary infarctions to the lower lobes and, more particularly, to the right lower lobe. The influence of gravity in the upright position is undisputed in the causation of basal congestion. Significant factors governing pulmonary arterial circulation were discussed by Dock (9) in his discussion of the apical localization of tuberculosis. The relation between the right ventricular pressure of 20 to 25 mm. of mercury systolic and 0 diastolic, and the intrathoracic pressure of -5 to -10 causes an effective pulmonary arterial pressure of 25 to 30 systolic and 5 to 7 diastolic. The mean pressure, Dock points out, is 15 to 18 mm. of mercury, or, in terms of a column of blood, would be 10 to 23 cm. This pressure is sufficient to cause an active circulation of blood in the lower portions of the lungs but the apical, higher areas of the lungs are excluded

to the center of the right ventricular cavity, presumably cannot be effectively supplied unless the dynamics are altered by putting the patient in a horizontal position. It would follow that a sluggish circulation postoperatively in cardiac decompensation, or in a confining illness, would primarily cause congestion in the lower lobes. With the explanation of hemodynamics given, it is inferred that relatively little blood flows through the upper lobes since patients are seldom completely recumbent. Therefore, the low incidence of infarction in the upper lobes might easily be explained as a consequence of the low blood supply and the resulting lesser degree of congestion which occurs in this area.

The problem of the predominance of right-sided infarction remains unexplained but it is of interest that the congestion of the right lung is usually more severe and appears earlier than on the left. This is demonstrated in cases of cardiac decompensation with hydrothorax. The fluid is almost exclusively situated on the right side. Apparent exceptions in which hydrothorax has been noted clinically on the left have been explained at necropsy. Adhesions of the visceral and parietal pleura in these cases have obliterated the potential pleural cavity on the right preventing the accumulation of fluid (3). Many hypotheses have been suggested to explain the high incidence of right hydrothorax but pulmonary engorgement is a *sine qua non* of all explanations (10). Thus an understanding of the pathogenesis of right hydrothorax is of utmost importance in any discussion of the predominance of infarction of the right lung.

Increased stasis especially on the right side is produced in heart failure as a consequence of enlargement of the right atrium and subsequent compression of the right pulmonary veins. These veins lie in close apposition to the right atrium and superior vena cava. While compression of the azygous system is important in the genesis of hydrothorax, it is not of significance in pulmonary congestion since the veins of the parietal pleura drain into this system but not the veins of the visceral pleura. It is pointed out by Dock (11), reviewing the anatomical factors in right hydrothorax, that patients with cardiac decompensation lie in the preferred right lateral recumbent position, causing a higher venous pressure in the right lung. The blood from the right lung must be lifted to the level of the left atrium in this situation while drainage from the left lung is aided. Congestion in the right lung is promoted greatly by this position. In the patient who develops pulmonary infarcts in the absence of cardiac failure, these factors may not be as pertinent.

The flow of blood through the pulmonary artery has received attention. Scherf and Schonbrunner (12) introduced masses of radio-opaque substances into the femoral veins of dogs. A majority of these masses were seen to lodge in the lower right lobe. In 2 of their experiments, 3 of 5 masses passed to the identical vessel. This work arouses speculation as to whether the pulmonary arteries may influence preferential flow of emboli to the right lower lobe. Text books of anatomy (13, 14) agree that the right branch of the pulmonary artery is larger and longer than the left. Small differences in diameter in these arteries may cause great differences in the volume flow of blood since the physical principle holds that the quantity of a fluid passing through a tube per unit of time is proportional

to the fourth power of the diameter (15) Strict physical laws cannot completely govern the division of pulmonary arterial blood flow because of such factors as variability of diameter, distensibility of the arteries, and the angles at which the arteries branch from the main pulmonary artery Consideration of the influence of the greater diameter of the right pulmonary artery, however, may afford an explanation of the fact that emboli seem to lodge more frequently in the right lung

The relation of the dual circulation of the lung to the problem is speculative for the most part Consideration of the anatomy, physiology, and pathology of the bronchial artery may contribute to the explanation of the predominance of right-sided pulmonary infarction As a rule, there is only one bronchial artery to the right lung which arises from either the first aortic intercostal artery or from the left bronchial artery In contrast, on the left side there are two bronchial arteries arising from the thoracic aorta (13, 14) The blood supplied through the bronchial arteries to the right lung is thus not as great as to the left lung This quantitative difference is of questionable major importance but it may be of significance as a contributory factor in the localization of pulmonary infarction to the right lung

In various pathologic conditions, the bronchial arteries may increase in size and carry a considerable portion of the blood to the lung Virchow (16) first demonstrated that after obstruction of a pulmonary artery there was an increased bronchial artery development By injecting radio-opaque substances into the bronchial arteries of cadavers and then examining the state of the arteries in various diseases, Wood and Miller (17) discovered that in lesions of the pulmonary vascular tree and in cardiovascular diseases, numerous bronchopulmonary artery anastomoses developed The anastomoses widened in all cases of increased pulmonary venous pressure Therefore, where the lung is predisposed to infarction by being severely congested, the bronchial artery supplies an increased portion of the blood to the lung It is possible that, because of the additional bronchial artery, the circulation to the left lung is more strongly fortified than to the right Obstruction of a smaller branch of the pulmonary artery on the left might not result in infarction while an embolus to a similar vessel on the right would result in the pathologic changes of infarction

The development of the bronchial artery progresses further in cases which are chronic Wood and Miller found that in cases of far advanced pulmonary tuberculosis the bronchial artery was greatly enlarged The increase of blood flow through the bronchial arteries in advanced tuberculosis would lead one to expect a low incidence of pulmonary infarction To compare the frequency of pulmonary infarction in tuberculosis to our general incidence of approximately six per cent of necropsies, protocols of 200 cases of advanced pulmonary tuberculosis were studied In this group, not one case of pulmonary infarction occurred Recently Fox, *et al* (18) studied 2,182 postmortem examinations in a hospital devoted completely to the treatment of tuberculosis In this large series, only 22 cases (one per cent) of pulmonary infarction were diagnosed They remark that this is a strikingly small number in an institution where bed rest is a funda-



mental therapeutic procedure. They explain the rarity of infarction in three ways: (1) the relatively young age group of the patients, (2) the exceedingly small number of patients in cardiac failure, (3) the predominant pathologic finding of thrombophlebitis which is said to embolize less frequently than phlebotrombosis.

There are undoubtedly other factors which influence and are responsible for this low incidence in tuberculosis. The changes in the bronchial arteries, however slight, invite speculation. If alterations in these vessels are responsible, in part, for a low incidence of infarction in tuberculosis, other conditions may also be effected similarly. Following this reasoning, the superior distribution of the bronchial arteries to the left lung may prevent so frequent infarction as on the right, where only one bronchial artery is present.

A better understanding of the pathologic physiology of pulmonary infarction and the reasons for its more frequent occurrence in the right lower lobe is essential for a rational approach to prevention of the phenomenon. With more attention focused on the reversible physiologic factors that are involved in the pathogenesis of infarction, necrosis of the pulmonary parenchyma might be avoided in some instances.

#### SUMMARY

It is shown that pulmonary infarction occurs most frequently in the right lower lobe. For many years, stasis in the pulmonary vascular system has been recognized as the primary predisposing factor in the development of infarction. By clinical and experimental investigation, confirmation of this fact exists. Increased congestion in the right lower lobe seems to account for the prevalence of infarction here. The pathological physiology which causes more pronounced stasis in this lobe has been reviewed. Other factors which may be of significance in the predominance of right lower lobe infarction have been considered. Among these are the preferential flow of emboli to the right lower lobe and a comparative decrease in bronchial artery blood supply to the right side. The rarity of pulmonary infarction in tuberculosis is emphasized and explained in so far as it may have bearing on understanding the genesis and localization of pulmonary infarction in the right lower lobe.

#### SUMARIO

##### *Sobre la Localización del Infarto Pulmonar*

Es sabido que el infarto pulmonar sobreviene más frecuentemente en el lóbulo inferior derecho. Por muchos años, ha sido reconocido que el éstasis del aparato vascular pulmonar es el factor predisponente primario en la producción del infarto, y así lo han confirmado las investigaciones clínicas y experimentales. La hipercongestión del lóbulo inferior derecho parece explicar la frecuencia del infarto allí. Después de repasar la patofisiología que ocasiona un estatismo más pronunciado en dicho lóbulo, considéranse otros factores que pueden revestir importancia en el predominio del infarto del lóbulo inferior derecho. Entre los últimos figuran el paso preferencial de émbolos a ese lóbulo, y la comparativa

disminución de la circulación de la arteria bronquial al lado derecho Recálcase la rareza del infarto pulmonar en la tuberculosis, explicándola en lo que pueda guardar relación con la comprensión de la génesis y localización del infarto en el lóbulo inferior derecho

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# FACTORS AFFECTING THE IN VITRO CYTOLYSIS OF WHITE BLOOD CELLS BY TUBERCULIN<sup>1 2</sup>

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## INTRODUCTION

Since Koch first introduced tuberculin as a "cure" for tuberculosis, much attention in the clinic and laboratory has been devoted to the role which the tuberculin type of allergy plays in human tuberculosis. Although a similar type of tissue reaction occurs following sensitization to substances from many other bacteria or parasites and has been studied in the field of sensitization to simple chemical compounds (1), the tuberculin type reaction still is taken as the prototype of the delayed types of tissue hypersensitivity.

The now classic tissue culture studies of Rich (2, 3, 4, 5) have shown that the tuberculin reaction is in some way related to the white blood cell types of the host. *In vitro* cultures of splenic explants from tuberculous guinea pigs, grown in plasma from normal animals, are destroyed by amounts of tuberculin non-toxic for normal animal tissue cultures. On the other hand, explants from anaphylactically sensitized animals are not damaged when exposed to homologous immune serum of sensitizing antigen (6). More recently Landsteiner has shown that the delayed type of sensitivity is transferable to a normal host when cells, but not serum, of a sensitized animal are used (1). Chase (7) and others (8, 9, 10) have extended this technique to the tuberculin reaction itself, thus still further implicating the white blood cell and not a serum antibody as the mediator in the tuberculin type reaction.

When the effect of tuberculin on white blood cells is studied in fluid suspensions rather than in the fixed cell masses of the tissue culture techniques, a similar cytotoxic effect of tuberculin is observed (11). Although this destructive effect of tuberculin on white blood cells has been noted on selected cases of human tuberculosis (12), little is known concerning the clinical conditions under which this phenomenon may be present. The present report is a study of a larger group of tuberculous subjects, as well as persons with other acute illnesses, by means of such an *in vitro* tuberculin cytotoxicity procedure. The findings in these patients constitute the body of the report which follows.

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## MATERIALS AND METHODS

For the sake of systematization, the patients studied have been grouped according to the accuracy of diagnosis and severity of illness. By these criteria, the subjects studied fall into five groups:

- 1 Active tuberculosis with systemic manifestations (fever, weight loss, cough, expectoration), clinical and roentgenographic evidence of disease and/or recovery of tubercle bacilli on culture
- 2 Active tuberculosis with little or no systemic manifestations (without toxic effects), clinical and roentgenographic evidence of disease
- 3 Obscure febrile illnesses with a self-limited course, positive PPD cytotoxic test during acute phase of illness
- 4 Other acute febrile diseases
- 5 Normal subjects with and without a positive cutaneous tuberculin reaction

*Method*

*Technique* One tenth ml. of heparin (Liquaemin 10 mg. per ml. in 0.85 per cent NaCl) and 0.05 ml. of 5 per cent dextrose are drawn into a 2 ml. syringe. Two ml. of blood (total volume 2.1 cc.) are then withdrawn by venipuncture without stasis, and the blood and heparin promptly mixed in the syringe with the aid of a bubble of air. A PPD (Purified Protein Derivative of tuberculin) (13) solution is prepared by dissolving one 25 gamma tablet of PPD in 0.5 ml. of 0.85 per cent NaCl (not phosphate buffer)<sup>6</sup>. Old Tuberculin<sup>®</sup> 0.1 ml. of a 1:30 dilution may be used in place of PPD and will give comparable results (table 1).

Four tenths ml. of the heparinized blood is put in each of two 1.0 cm. diameter Kahn tubes which have been shortened to 4 cm. lengths for ease in white count pipetting and which have been coated with organosilicon (14) to diminish nonspecific cytotoxicity. One tenth ml. of PPD solution is added to one tube and 0.1 ml. saline to the other. The tubes are immediately shaken by hand for three minutes and a white blood count is done with a mechanical pipette filler<sup>7</sup> and calibrated pipettes. Fifteen squares on 2 chambers of the standard hemocytometer slide are counted. These two counts are the five minute counts indicated in the tables. The tubes are stoppered and rolled slowly in an incubator at 37° C. for one hour. They may be shaken continuously during this time if a shaker is available or at the end of an hour should again be shaken by hand for three minutes before recounting. Adequate terminal shaking is essential for accurate counts. Likewise, a minimum constant speed of shaking the pipette after adding acetic acid, preferably by a mechanical shaker, is desirable. A positive cytotoxic test will show a fall in the white blood count in the presence of tuberculin and not in the presence of saline. In the hands of careful technicians who follow these precautions scrupulously, the "technical error" can be below 5 per cent (table 5). Detailed data on the different groups studied are given to support this conclusion.

*Clumping* When fresh white blood cells are placed in a noxious environment, the neutrophils, especially those of the sick patient, tend to clump together or adhere to surfaces. This reaction might well be expected since intravital dye morphological studies of white blood cells taken from patients with active tuberculosis show alterations in granular content and increased vacuolation (15). In specific tuberculin cytotoxicity, the clumping tendency observed is roughly proportional to the specific cytotoxic effect of tuberculin. Appropriate

<sup>6</sup> Phosphate or citrate ions will block specific tuberculin cytotoxicity.

<sup>8</sup> O. T. was dialyzed for six days against frequent changes of 0.85 sodium chloride and made up to a 1:30 dilution calculated on the basis of the original volume of crude O. T.

<sup>7</sup> Automatic suction apparatus, Clay Adams Company.

TABLE 1  
Group I *Active Tuberculosis*  
*Positive Cytolysis Test*

	DATE	WBC PER CU MM	PER CENT FALL SALINE	PER CENT FALL PPD	PPD DECRE- MENT	CULTURE*	COMMENT
M S	2-22-48 3- 1		-4 0 -4 5	-29 5 -27 6	-35 5 -23 1	G+, S+	Acute exudative pulmo- nary tuberculosis
Ro P	5-24 5-26 5-28 6-18 6-24 6-26 7-12 7-22 7-29	3,590 4,200 3,740 5,060 5,500 2,910 5,570 3,940	-0 -1 0 -4 0 -2 7 -3 1 +0 7 +1 7 -2 1	-33 4 -46 5 -47 5† -34 0† -36 1† -46 5† -20 4 -34 7†	-33 4 -45 5 -45 5 -31 3 -33 0 -45 8 -18 7 -32 1	S+         	Tuberculous broncho- pneumonia      Streptomycin started  Poor response to strepto- mycin
A B	6-18 6-23	6,300 6,800	-1 8 -0 5	-27 0 -15 1	-28 8 -14 6	Pl f +	Acute pleurisy with effu- sion
W C	6- 2 6- 4	7,390 8,600	-1 0 -0 3	-14 8 -19 9	-13 8 -19 6	S+, G+	Acute exudative pulmo- nary tuberculosis
Ri P	2-18 6-12 9-28 9-29	3,270 9,360 6,850	0 -2 5 +0 7	-2 2 -15 6 -14 7	-2 2 -13 1 -15 4	G- G+ G+	Tuberculoma of lung Tuberculoma with cavity 3 months pregnant
M M	9- 7 9- 9 10- 5 11- 5	8,130 7,030 6,490 8,700	-0 7 +1 0 +0 5 -2 2	-9 6 -15 3 -41 7† -35 3	-8 9 -14 3 -42 2 -33 1	S+	Acute exudative pulmo- nary tuberculosis, far advanced, tuberculous bronchitis and laryngi- tis
H K	10-11 10-14 10-14 10-16 11- 2 11-15 11-17 11-22	8,050 6,830 6,800 4,870 3,360 6,720 4,560 5,960	-4 1 -0 7 -0 7 -0 7 -1 1 -2 0 -0 7 0	-21 8 -26 8 -22 8† -14 5† -29 7† -29 7 -21 7† -15 0†	-17 7 -26 1 -22 1 -13 8 -28 6 -27 7 -21 0 -15 0	S+	Acute exudative pulmo- nary tuberculosis, mod- erately advanced
G C	11- 9 11-10 11-23	7,840 8,560 5,650	-0 5 -1 1 +0 7	-25 7 -31 8 -22 4†	-25 2 -30 7 -23 1	Biopsy+	Mesentery adenitis, tu- berculous, rheumatoid arthritis, active
T D	4-20 4-22 10- 2	12,450 12,450 6,150	-5 6 -3 4 -1 0	-26 5 -37 3 +0 5	-20 9 -33 9 +1 5	G-	Acute pleurisy with effu- sion Well

TABLE 1—*Continued*

	DATE	WBC PER CU MM	PER CENT FALL SALINE	PER CENT FALL PPD	PPD DECRE MENT	CULTURE*	COMMENT
W M	6-25	6,490	-6 2	-38 0	-31 8	G— Pl fl —	Acute pleurisy with effu- sion Began streptomycin treat- ment
	6-29	6,530	+0 5	-17 4	-17 8		
	7-11						
	7-14	7,470	-0 7	-2 4†	-1 5		
	7-22	6,580	0	+1 2	+1 2		
M E	6-22	6,510	-9 9	-36 7	-26 8	G—, S—	Acute exudative pulmo- nary tuberculosis
	6-25	5,180	-2 3	-16 8	-14 5		
	6-29	4,270	-1 5	-20 6	-19 1		
C H	6-29	15,000	-1 8	-26 0	-24 2	G—, S—	Acute exudative pulmo- nary tuberculosis
	7- 1	19,700	-16 2	-34 1	-17 2		
	7- 6	14,410	-0 5	-39 3	-38 8		
N S	7-15	4,660	0	-31 2	-31 2	G—, S—	Acute exudative pulmo- nary tuberculosis
	7-27	5,560	-2 3	-39 0†	-35 7		
	7-27	5,560	-0 6	-34 8	-34 2		
W J	5- 6	3,940	-1 6	-25 7	-24 1	G—, S—	Acute exudative pulmo- nary tuberculosis
	5-11	6,000	-4 6	-14 1	-9 5		
	5-14	8,490	-1 7	-25 2	-23 5		
L C	6-25	5,460	-1 7	-38 7	-32 0	G—, S—	Acute exudative pulmo- nary tuberculosis
	6-29	4,750	+2 0	-20 5	-22 5		
G L	11-16	6,170	-1 0	-32 2	-31 2	G—	Exudative pulmonary tu- berculosis, minimal, ac- tive
	11-17	5,190	-0 5	-22 7	-22 2		
	12- 1	5,070	+1 2	-4 1	-5 3		

\* G—gastric aspiration cultured, S—sputum cultured, Pl fl —pleural fluid cultured

† O T—See text

tuberculin controls on normal white blood cells and antigen controls on the patient's blood with a streptococcus protein<sup>8</sup> indicate that this phenomenon is a part of the cytotoxic effect itself and not an artifact. A similar clumping tendency has been found in association with the alarm reaction to be discussed in this paper. This clumping tendency has been offset satisfactorily by keeping white cells under as nearly physiological conditions as possible. Adequate glucose is present, glassware is chemically clean, sterile saline suitable for intravenous use is employed, and tubes are stoppered to prevent shifts in pH due to evolution of carbon dioxide.

The cytotoxic effect of tuberculin takes place in 20 minutes to one hour and changes little thereafter. In a positive reaction, from 10 to 40 per cent of leukocytes are destroyed in this interval. In man the small mature lymphocytes and the neutrophils are the cells lost. If

<sup>8</sup> This material is obtained from beta hemolytic streptococcus by formamide extraction. It produces a delayed-type intracutaneous reaction in subjects who have recently had a streptococcal infection. It also causes a disease-specific *in vitro* cytotoxicity when used by the method described in this report. The details of its preparation and its relation to clinical disease will be presented in a separate communication.

their percentage fall is great in this period, a further fall may be anticipated. In general, however, counts done at 90 and 120 minutes agree closely with the 60 minute counts

## RESULTS

*Active tuberculosis* In table 1 (Group I) there are listed a selected group of patients who have been studied during hospitalization for tuberculosis. Each

TABLE 2  
Group II *Active Tuberculosis*  
*Negative Cytolysis Test*

	DATE	WBC PER CU MM	PER CENT FALL SALINE	PER CENT FALL PPD	PPD DEC- REMENT	CULTURE*	COMMENT
W Mc	6-8-48 7-6	6,240 6,660	-3.7 -3.7	-1.0 -3.5	+2.7 +0.2	S-, G-	Pulmonary tuberculosis, minimal, active
A M	7-7 7-8	4,530 4,020	-5.3 +1.0	-0.7 -3.0	-4.0 -2.2	S+	Pulmonary tuberculosis, moderately advanced with cavitation
M G	3-8	2,210	+5.5	+4.0	+1.5	G+	Pulmonary tuberculo- mas, pleural effusion, controlled diabetes mellitus
R A	9-7 9-9	6,770 5,120	-0.7 -1.8	-0.7 -1.5	0 +0.3	S+	Pulmonary tuberculosis, moderately advanced
O F	9-7 9-9	4,560 3,670	0 -1.7	-0.9 +1.2	-0.9 +3.9	S+	Pulmonary tuberculosis, moderately advanced
L M	9-7 9-9	6,390 3,130	-2.2 -0.7	-7.0 -5.0	-4.8 -4.3	S+	Pulmonary tuberculosis, moderately advanced
B S	9-21 9-23	7,650 5,490	+0.3 -1.5	-0.4 -1.5	-0.7 0	G+	Pulmonary tuberculosis, moderately advanced
E S	9-22 9-23	8,530 9,780	0 -0.6	-1.8 0	-1.8 +0.6	D+	Tuberculosis of spine with draining psoas abscess

\* S—sputum cultured, G—gastric aspiration cultured, D—drainage cultured

person ran a degree or more of temperature elevation and, in addition to the laboratory findings indicated in the table, appeared to be acutely ill. White cell studies were done two or more times on different days. It will be observed that PPD decrements<sup>9</sup> varied in the same and in different patients but were greater than 10 per cent in each individual. The sicker the patient, the greater the PPD

<sup>9</sup> PPD decrement is the difference between the per cent fall in white count in saline and in PPD solution

TABLE 3  
Group III *Other Diseases*  
*Positive Cytolysis Test*

	DATE	WBC PER CU MM	PER CENT FALL SALINE	PER CENT FALL PPD	PPD DEC- REMENT	COMMENT
A M	7- 8-48	5,520	+0 7	-23 6	-24 3	Post-sedation atelectasis and fe- brile bronchitis Recovered
	7- 9	4,850	+0 5	-32 7	-33 2	
	7-26	5,560	0	-6 1	-6 1	
M W	9-10	4,640	-8 5	-25 3	-16 8	Age 80, negative physical exam- nation and laboratory findings
	9-11	5,390	+2 0	-12 3	-14 3	
	9-13	6,380	-7 7	-18 7	-11 0	
A C	9-10	3,790	-9 5	-14 6	-5 1	Fever of unknown origin, 5 weeks  Temperature normal 3 days after streptomycin treatment
	9-11	5,850	+2 2	-13 8	-16 0	
	9-13	5,140	-1 4	-19 5	-18 1	
	9-21	6,780	-4 2	-4 2	0	
W B	9-30	11,100	0	-10 0	-10 0	Myocardial infarction with con- gestive failure, mural thrombus and cerebral embolus -23 0 with Brucellergin One pint pus from iscial abscess drained 10-1 (E coli, proteus, A aerogenes) -44 2 with Brucellergin
	10-1					
	10- 4	8,400	-0 7	-8 2	-7 5	
H O'C	9-13	5,870	-2 1	-56 7	-54 6	Renal colic
	9-14	5,740	+1 4	-28 0	-29 4	
	9-16	4,880	+1 1	-35 2	-36 3	
	9-18	5,800	-2 3	-27 6*	-25 3	
	9-21	5,190	-1 5	-13 3	-11 8	
	10- 2	5,100	-2 2	-15 5	-13 3	
	10-11	3,870	0	-2 3	-2 3	
P G	10-24	7,450	-5 0	-8 2	-3 2	Pulmonary infarct in an area containing calcified hilar lymph nodes
	10-27					
	10-29					
	11-13					
	11-26					
	12- 3	6,730	+0 3	+0 3	0	Recovered

\* O T—See text

decrement On the other hand, the PPD decrement was below 10 per cent during relatively quiescent phases of the patient's course (R P, M M) or coincident with obvious clinical improvement (T D, W M)

In table 2 (Group II) are listed patients with active tuberculosis whose blood showed a negative cytotoxic test with PPD The lesions vary from minimal pul-  
monary tuberculosis (W Mc) through moderately advanced disease (A M) to a



TABLE 4  
Group IV *Other Diseases, no Alarm Reaction*  
*Negative Cytolysis Tests*

	DATE	WBC PER CU MM	PER CENT FALL SALINE	PER CENT FALL PPD	PPD DECRE- MENT	DISEASE
P DeP	7- 2-48 7- 6	5,360 5,650	+0 5 -6 0	+0 8 -4 3	+0 3 +2 3	Acute febrile bronchitis
R G	7- 2 7- 6	4,920 5,300	-0 5 -3 0	-1 2 +1 0	-0 7 -4 0	Acute upper respiratory infection
J Fan	7- 6 7- 7	9,220 6,700	0 -1 0	-4 0 0	-4 0 -1 0	Lung abscess
A P	7-16 7-22	4,930 5,280	-5 7 -2 5	-3 6 -1 0	+2 1 +1 5	Carcinoma of lung with second- ary infection
K L	7-22 7-28	7,390 11,400	-0 7 -5 0	0 -5 0	+0 7 0	Virus pneumonia
S M	9- 9 9-10	8,900 9,850	-1 0 -0 1	+0 5 -0 3	+1 5 -0 2	Asthmatic bronchitis, broncho- pneumonia
R B	7- 8 7- 9	6,550 5,800	-1 0 -2 5	-5 5 -0 5	-4 5 +2 0	Prostatic obstruction, acute pye- lonephritis
D G	7-26 7-28	5,680 6,330	-5 8 -5 1	-2 7 -4 8	+3 1 +0 3	Acute myocardial infarction, fifth day
J F	9-23 9-21	7,610 11,480	-0 5 -0 5	0 +0 2	+0 5 +0 7	Chronic febrile bronchitis
A H	9-21 9-22	3,820 4,270	+1 0 -1 0	+1 2 -1 2	-0 2 -0 2	Virus pneumonia with asthma, recovering

*Other Diseases, with Alarm Reaction*  
*Negative Cytolysis Tests*

J K	7- 2 7- 8	11,600 9,650	-12 0 -33 8	-10 7 -34 0	+1 3 -0 2	Acute asthmatic bronchitis, status asthmaticus
A B	7-22 7-26	5,070 5,630	-16 3 -2 6	-20 2 +1 0	-3 9 +1 6	Virus pneumonia, severe
A S	9-10 9-13	36,900 27,300	0 -21 7	-1 5 -21 5	-1 5 +0 2	Carcinomatosis, bronchopneu- monia
M R	9-10 9-11 9-14	11,020 9,910	-22 4 -20 1	-21 2 -21 5	+0 8 -1 4	Fulmantent meningococcus men- ingitis Died
L R	9-10 9-13 9-17	4,370 5,120 7,140	-3 4 -22 5 -0 4	-8 8 -21 6 +0 7	-5 4 -0 9 +1 1	Virus pneumonia, severe, migrat- ing type
E M	7-16 7-17 7-20 9-16	14,500 10,600 12,500 5,730	-0 9 -7 0 -11 3 -2 9	-1 0 -5 8 -10 7 -1 6	-0 1 +0 2 +0 6 +1 3	Staphylococcus osteomyelitis One day postoperative Well
A J	9-16 9-17	6,010 4,310	-5 0 -1 2	-4 5 -0 8	+0 5 +0 4	Pleurisy with effusion

TABLE 5  
Group V Normal Subjects

	DATE	WBC PER CU MM	PER CENT FALL SALINE	PER CENT FALL PPD	PPD DECRE- MENT	PREVIOUS PPD SKIN TEST		COMMENT
						First	Sec ond	
E M	3-11-47	4,520	-1 8	+0 3	-2 1	-	+	
J B	3-23-48	4,460	-3 5	-5 4	-1 9	-	+	
E P	2-15 7- 1	5,080 4,520	-2 0 +0 5	+2 0 0	+4 0 +0 5	-	+	
M W	6-30 7- 1	4,980 3,255	0 0	-1 2 +3 1	-1 2 +3 1	-	-	
S J	6-30 7- 1	6,460 6,000	-0 2 +1 3	+1 1 -3 9	+1 3 -4 2	-	-	
R T	6-30 7- 1	6,180 5,870	+1 5 -0 5	-0 -0	+1 5 +0 5	-	-	
G M	7- 7 7- 8	3,770 3,810	-1 6 0	0 -1 3	+1 6 -1 3	-	±	
M Z	7-15 7-16	3,610 5,570	-2 2 -1 5	-0 7 -1 5	+1 5 0	-	+	
LeC	7-28	5,870	-3 1	-2 5	+0 6	-	+	
J B	9-28 9-29	5,740 4,340	-3 1 -0 8	0 0	+3 1 +0 8	-	+	
J E	10- 4 10- 7	6,240 5,590	0 -3 9	-2 0 +1 0	-2 0 +4 9	-	+	
C B F	3-15 6- 3 6- 3 6- 4 6- 7 6- 9 9-13	4,520 5,310  5,500 3,410 4,020	+2 5 -3 6  -1 5 -3 8 -0 8	+3 0 -3 5  -27 0 +1 1 -0 3	+0 5 +0 1  -25 5* -4 9* -1 1	-	+	Second strength PPD placed +++ local reaction
J M	7-16 7-19 7-19 7-20 7-22 9- 9	6,950 6,410  6,540 8,900	-0 6 -0 6  -1 0 -1 0	0 -1 0  -0 6 +0 5	+0 6 -0 4  +0 4 +1 5	-	+	First strength placed Second strength placed ++ reaction
J V	9- 8 9-13 9-15 9-16 9-18 9-20 10- 2	3,360 3,490  5,470 4,480 4,230	-1 5 -0 4  -2 5 -1 2 0	-0 6 -3 0  -18 2 -0 6 -2 1	+0 9 -2 6  -15 7* +0 6 -2 1	-	+	First strength placed Second strength placed +++ reaction
B W	7- 9 7-12 11-10 11-12 11-13 11-14	5,470 3,630  3,080	-0 5 +0 7  -2 5	-1 0 -2 0  -2 5	-0 5 -2 7  0	-  -	-	First strength placed Second strength placed - negative reaction
M U	7- 9 7-12 11-10 11-12 11-13 11-14	4,770 4,600  4,460	0 +0 5  +0 7	-1 7 -1 4  +1 5	-1 7 -1 9  +0 8	-  -	-	First strength placed - Second strength placed - negative reaction

\* Values not included in calculation of standard deviation of the mean

Using the formula  $\sigma = \frac{\epsilon(x^2)}{N}$  for the PPD increments on the above data,  $2\sigma = 3.9$  blood may be lower than that for blood from sick patients Twice the standard deviation of the mean of normals is 3.9

poas abscess which had been draining for two years (E S) None of these patients had more than a degree of fever and all maintained their weight and their feeling of well being It will be seen that all the PPD decrements were below 10 per cent

In table 3 (Group III) are listed patients with widely differing acute illnesses The PPD decrements vary from 10 per cent in a man with a myocardial infarction (W B) to 54 per cent in a young house officer with agonizing renal colic (H O'C) Careful studies over many months have failed to reveal the presence of clinical tuberculosis in any of these persons Four of the patients had PPD decrements below 10 per cent coincident with recovery (A M, A C, W B, H O'C), and one showed no signs or symptoms other than extreme age (M W) All had positive intracutaneous reactions to first or second strength PPD (tested after cytolysis studies) The cause for these changes is obscure

In table 4 (Group IV) are listed a series of duplicate studies on persons with a wide variety of acute illnesses Some of these persons have had simple difficulties (P DeP, R G), others have had dramatic illnesses (J Fran, D G)

Some patients (Group IV) show an "autodestruction" of lymphocytes in whole blood This may be an *in vitro* "alarm reaction" similar to the phenomenon induced in the intact host by the adrenocorticotrophic hormone (ACTH) of the pituitary gland (16, 17)

In table 5 (Group V) are given the values for PPD and saline control white blood counts on normal subjects with and without a positive cutaneous reaction to tuberculin With the exception of the PPD decrements occurring within several days following a strongly positive cutaneous tuberculin reaction (C B F, J V), the values are low When values not starred are subject to statistical analysis, twice the standard deviation of the mean is 3.8 It should be noted that this finding is for normal white blood cells existing under relatively ideal conditions for survival The error of the method as applied to the effect of PPD on abnormal white blood cells may be as much as 5 per cent, as may be seen in Group I (table 1) in the day to day variations of a given patient whose clinical course is stationary (Ro P, H K)

*False positive reactions* The careful study of several patients who had PPD decrements of 14 to 25 per cent in their cytotoxic test on repeated observations, and who were found to have no tuberculosis by clinical criteria, cultures, or by autopsy, led to the finding that the induction of a positive tuberculin skin test may be associated with an *in vitro* tuberculin cytotoxicity in the patient's blood when tested several days afterwards This is also true in some healthy tuberculin-positive persons who normally have a negative tuberculin cytotoxicity test and yet show a transiently positive white cell test after administration of PPD intradermally (Group V, table 5)

Certain persons with acute febrile illnesses of a nontuberculous nature have shown a transient PPD decrement (Group III, table 3) This decrement has returned to zero upon recovery Cultural and clinical evidence of tuberculosis has been absent in such patients both during the acute illness and subsequently In several of these individuals an obvious bacterial infection has been present, for example a carbuncle, where a greater cytotoxicity to staphylococcus protein than

to PPD was observed. The majority of the miscellaneous acute illnesses studied (Group IV, table 1) have not shown this nonspecific effect. This type of false positive reaction is possibly an anamnestic effect of the acute infectious process upon subclinical tuberculosis.

#### DISCUSSION

The observations reported in this paper indicate that few of the circulating white cells in homologous plasma of tuberculin positive "normal" people or of persons with chronic tuberculosis are affected by tuberculin. Even in highly active tuberculosis only a portion of the peripheral white cells are destroyed by tuberculin under the conditions of these experiments. By the same token, in none of the examples of highly active tuberculosis have we found a correlation between *in vitro* cytotoxicity and the size of the cutaneous tuberculin reaction. The earlier tissue culture type of experiment indicates that tuberculin causes greater white cell damage than we have observed and, if anything, the lymphocyte is the most frequent surviving cell type at the end of 24 hours. It should be remembered, however, that such experiments were conducted in static media free of homologous plasma, consisted of 24 to 48 hour observations on cell systems having a low survival of some cell types, especially the neutrophils, and were in no way quantitative estimates of cell populations. As one-half or more of the lymphocytes from peripheral blood survive the first hours of exposure to tuberculin *in vitro* as measured by the cytotoxicity test, and as lymphocytes are known to live up to three or four days in tissue culture, it is not surprising that discrepancies between the findings of cytotoxicity tests and tissue cultural methods exist.

The observation that a positive tuberculin test may be followed by a greater PPD decrement in the white cell lysis test sheds some light on the mechanism of activation of tuberculosis foci by an excessive injection of tuberculin, or the activation of a remote lesion by a local tuberculous process. In the same way, the presence of a positive tuberculin cytotoxicity test, as for example in persons with progressive tuberculosis, may indicate a recent liberation of tuberculin substances somewhere in the host. Likewise the reversion of the tuberculin cytotoxicity test to negative at the time clinical symptoms are ameliorated suggests that the local liberation of tuberculin has become minimal. It is of interest in this connection that we have observed the disappearance of the positive tuberculin cytotoxicity test coincident with clinical improvement in tuberculous pleurisy with effusion, and with the temperature fall after successful treatment of tuberculous pericarditis with streptomycin. The presence of an "anamnestic-like" tuberculin cytotoxicity test coincident with other acute disease suggests several interesting possibilities. For one thing, such undiagnosed febrile illnesses may be true active tuberculous infections which are promptly controlled by a relatively resistant host, or they may be inapparent minimal tuberculous "spreads" during intercurrent infections. Reactions of this sort also suggest a mechanism whereby one acute infection may activate a quiescent tuberculous focus of infection.

#### SUMMARY

1. A portion of the white blood cells in heparinized whole blood from patients acutely ill with tuberculosis is lysed by tuberculin (PPD) *in vitro* within one hour.

2 This phenomenon bears a rough correlation with focal allergic manifestations of the tuberculous process but not with the degree of the cutaneous reaction to tuberculin

3 The mechanism of the tuberculin reaction is briefly discussed

#### SUMARIO

##### *Factores que Afectan la Citolisis in Vitro de los Leucocitos por la Tuberculina*

1 Cierta porción de los leucocitos en la sangre íntegra heparinizada de los sujetos agudamente enfermos con tuberculosis es lisada por la tuberculina (PPD) *in vitro* en término de una hora

2 Este fenómeno guarda una tosca correlación con las manifestaciones alérgicas focales del proceso tuberculoso, pero no con la intensidad de la cutirreacción a la tuberculina

3 Discútese brevemente el mecanismo de la reacción tuberculínica

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# A SIMPLIFIED GUINEA PIG TEST FOR TUBERCULOSTATIC AGENTS<sup>1</sup>

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## INTRODUCTION

The discovery of active chemotherapeutic agents in the field of tuberculosis has been made possible by testing them in experimentally infected animals. The need for tests requiring relatively small amounts of chemicals and short periods of testing has resulted in the development of new methods (see review by M I Smith (1)). Despite certain advantages of these, it seems that the classic guinea pig test is still indispensable in experimental tuberculosis work. With H G Wells and E R Long (1932), one "may feel quite sure that a drug which cures the disease in the guinea pig, or even influences it favorably, would more certainly be beneficial in the much less susceptible human being" (2). This view has been well confirmed by the success of the work initiated by Rich, Feldman and Hinshaw (3, 4) and others. As applied by these authors, however, the guinea pig test is applicable to the testing of only a few substances because of the need for large doses, long periods of testing, and large groups of animals.

An attempt has been made to simplify the guinea pig test without sacrificing its high degree of specificity. The results obtained during a four year period with a modification of the method are reported at this time, as others might wish to avail themselves of the test.

## MATERIALS AND METHODS

### *Basic Principles of the Test*

Preliminary studies of the experimental tuberculous infection of the guinea pig and its reaction to known tuberculostatic drugs, in particular 4,4'-diaminodiphenylsulfone, have formed the basis for the modification of the guinea pig test.

Like other investigators (5), we have learned that measurement of the degree of anatomical involvement is as good a criterion of tuberculostatic action as evaluation of the spread of the tubercle bacillus by culture methods. Survival tests with their requirements for large groups of animals, large quantities of chemicals, and long periods of experimentation, are reserved for substances which have proved their value in the test based on evaluation of anatomical involvement.

Study of the morphology of the primary focus in the experimental tuberculosis of the guinea pig reveals its tendency to spontaneous retrogression. This takes place, without any treatment, while the general disease progresses. This suggests the superiority of a test based on evaluation of a generalized infection. It would seem that the progress of the disease rather than the behavior of a primary focus

<sup>1</sup> From the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York, and Summit Park Sanatorium, Pomona, New York.

or involvement of a single organ (omental test) should be used to evaluate tuberculostatic action

Investigation of the tuberculostatic activity of 4,4'-diaminodiphenylsulfone has demonstrated the value of this substance as a standard for such activity in each single test. As this compound shows significant activity even after generalized infection has been already established, its use as a standard has helped shorten the period of testing. Furthermore, establishment of a standard of reference has made possible a well-defined tuberculostatic guinea pig unit. This unit is given by the minimal dose of any substance which has a tuberculostatic effect equal to that of the standard preparation of 4,4'-diaminodiphenylsulfone (50 mg daily) under the conditions of the test. For the study of the relation between chemical constitution and tuberculostatic activity, the definition of such a unit would seem most useful.

In the scheme for evaluation of anatomical involvement, equal consideration has been given to the extension of the infection through the lymphatic system and to hematogenous spread. Inoculating dose, mode of inoculation, and the type of infecting organisms have been chosen in such a way as to ensure a progressive type of infection (50 per cent of the animals dead within eight to ten weeks) but one which may be significantly retarded by a tuberculostatic agent. Retardation, not cure of the disease, has been the aim in the development of this short routine guinea pig test, devised primarily for the screening of tuberculostatic agents.

### *Description of the Test*

*Experimental animals* Guinea pigs of either sex and of the approximate age of two months, weighing between 300 and 350 Gm. at the start of the experiment, have been found satisfactory. To make certain that the animals are in good condition for the test, they are kept in the animal house for several days prior to inoculation. Usually 100 animals are inoculated for one test and are divided into groups of ten.

*Diet of experimental animals* The basis of the diet is formed by ground guinea pig pellets to which ascorbic acid 0.2 mg. per Gm. and ViDelta (1:10 dilution), containing 20 I.U. of Vitamin A per Gm. and Vitamin D 2.0 mg. per Gm., are added. Greens are added in the form of lettuce and spinach to the daily ration of 20 Gm. ground pellets.

*Preparation of inoculum* In all experiments a strain of human tubercle bacilli (Summit Park #4313) has been used. This strain was isolated in 1942 from a patient suffering from far advanced pulmonary tuberculosis. In guinea pig tests for virulence, this strain was found to be the equal of strain H37Rv. The Summit Park strain has the morphological and cultural characteristics of *M. tuberculosis* var. human and sensitizes guinea pigs to tuberculin. Both subcutaneous and intraperitoneal inoculation of various doses of this strain cause tuberculosis in the guinea pig of the classic Villemin type.

The strain has been cultured on egg media (whole egg 750 cc., egg yolk 150 cc., potato glycerin broth 600 cc.,  $\text{KH}_2\text{PO}_4$  10 per cent 15 cc., 2 per cent Malachite Green 18.75 cc.) and passed through guinea pigs twice a year. Third transplants from egg media between one and three months old have been used for preparation of the inoculum. The strength of the suspension in one-fifteenth molar  $\text{Na}_2\text{HPO}_4$  is determined by counting the number of bacilli contained in 0.05 cc. of the fluid placed on a slide marked with a square centimeter. The suspension is diluted to a strength of 100,000 organisms per 0.1 cc.

*Mode of inoculation* For inoculation the intraperitoneal route is used. It gives rise to a generalized infection faster than subcutaneous inoculation and allows exact measurement of the size of the primary lesion (omentum). The absence of fistulas, which commonly

develop after subcutaneous infection is desirable from the viewpoint of safety of the personnel handling the animals. The standard dose of inoculum has been fixed at 200,000 microorganisms. The inoculated animals are rotated in such a way that errors of dosing of the inoculum because of clumping in the syringe will be evenly distributed over the ten groups. Under the assumption that each group may have received an inoculum of different size, animals of each group of ten are distributed one each into ten new groups.

*Drug administration* Drugs are administered either in the diet, orally through a syringe, or subcutaneously. When given in the diet, the drugs to be tested are given in the 20 Gm of ground pellets described above. Feeding cups are constructed in such a way as to prevent excessive loss of the diet. The standard preparation of 50 mg 1,4'-diaminodiphenylsulfone is contained in 10 Gm of this diet and placed in the dish on top of 10 Gm of the same diet free of the drug.

For testing at the level of the standard, a total amount of 10.5 Gm of chemical is the minimum requirement. For comparison with streptomycin an amount of 4.2 Gm of substance is needed.

*Course of experiment* Drug treatment is started two weeks after inoculation and is continued for three weeks. The animals are weighed twice a week. They are sacrificed five weeks after inoculation.

*Evaluation of anatomical findings* The anatomical findings are evaluated according to the following scheme:

#### Omentum

No tubercles grossly	negative
Tubercles present, weight below 1 Gm	+
Tubercles present, weight between 1.0 and 2.0 Gm	++
Tubercles present, weight between 2.1 and 3.0 Gm	+++
Tubercles present, weight above 3.0 Gm	++++

#### Spleen

No gross lesions visible	negative
Few gross lesions, visible with difficulty	+
Definite gross lesions	++
Numerous gross lesions	+++
Innumerable gross lesions	++++

#### Liver and lungs

Same as spleen

#### Cervical lymph nodes

No tubercles visible	negative
Few tubercles, limited to 1 node	+
Few tubercles in 2 nodes	++
Tubercles in 2 nodes with enlargement of node	+++
Tubercles in 2 nodes with very marked enlargement	++++

#### Mediastinal lymph nodes (include retrosternal, tracheobronchial, bronchomediastinal nodes)

No tubercles grossly	negative
Tubercles present, weight below 0.6 Gm	+
Tubercles present, weight between 0.7 and 1.2 Gm	++
Tubercles present, weight between 1.3 and 1.8 Gm	+++
Tubercles present, weight above 1.8 Gm	++++

#### Abdominal lymph nodes (include gastric, portal, pancreatic, mesenteric, mesocolic)

No tubercles grossly	negative
Tubercles present, weight below 0.8 Gm	+
Tubercles present, weight between 0.9 and 1.6 Gm	++
Tubercles present, weight between 1.7 and 2.4 Gm	+++
Tubercles present, weight above 2.4 Gm	++++

Retroperitoneal lymph nodes Same as grading of mediastinal nodes



This scheme is easy to learn and has given identical results on the same material examined by two independent observers

*Calculation of tuberculous index* Every plus sign has the value of 25 per cent. The index of an individual animal is found by adding the indices of all eight organs mentioned in preceding paragraph. The group index is calculated by adding the individual indices and dividing the sum by the number of animals in the group (usually 10)

*Recording of data* All data pertaining to the experiment are recorded on one sheet for each animal, including signs of toxic reactions and other clinical observations

## RESULTS

As already mentioned, the purpose of the test has been twofold: first, to screen chemicals for tuberculostatic action by comparing them with a standard at the same level; secondly, to establish the unit value as defined above to learn about the relation between chemical constitution and tuberculostatic activity. Most of the work has been concerned with screening, the results of which are the subject of separate publications. It might be mentioned here that the results agree well with those of other investigators using longer and more complicated tests. A more de-

TABLE 1

DRUG	MODE OF ADMINISTRATION	GUINEA PIG UNIT
		mg
4,4'-diaminodiphenylsulfone	In the diet	50
Same	Subcutaneously	25
Streptomycinhydrochloride	Subcutaneously	20
4-aminophenyl-pyrazylsulfone	In the diet	100
4-aminophenyl-methylsulfone-hydrochloride	In the diet	200
Promin	In the diet	300

tailed study of some active compounds led to the establishment of their unit value (table 1)

In evaluating the usefulness of this modification of the guinea pig test, an attempt was made to get a correct picture of its accuracy and of the significance to be attached to deviations from the control index. This index was found in 46 experiments to range from 46 to 67 per cent, the mean being 57 per cent. The standard deviation was 4.2, the variation coefficient 9.1 per cent, the standard error 0.62. In the same group of experiments the average index of the groups, treated with the standard, 4,4'-diaminodiphenylsulfone, was 37 per cent with a range from 26.5 to 47 per cent. The standard deviation was 7.9, the variation coefficient 17.2 per cent, the standard error 1.16. It seems of importance that the extremes of range given here were found at a time when the technical aspects of the test had not yet been perfected. Furthermore, a tendency of the control index towards one extreme is accompanied by the same tendency of the index of the standard group.

## SUMMARY

Because of the necessity for a highly specific test for tuberculostatic agents which could be used with only small quantities of new chemicals, a modification

of the classic guinea pig test has been developed. Its execution, accuracy, and purpose have been discussed. The test requires five weeks for completion.

#### SUMARIO

##### *Simplificada Prueba en el Cobayo para las Sustancias Tuberculoestáticas*

Debido a la necesidad de contar con una prueba muy específica para las sustancias tuberculoestáticas, que pueda usarse con pequeñas cantidades de nuevos productos químicos se ha elaborado una modificación de la clásica prueba en el cobayo. Discutense aquí la ejecución, exactitud y propósito de la misma. La prueba requiere cinco semanas para completarla.

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# AN EVALUATION OF A METHOD OF OBTAINING GASTRIC WASHINGS<sup>1 2</sup>

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## INTRODUCTION

Examination, culture, and animal inoculation of the gastric contents of patients suspected of having pulmonary tuberculosis has long been an accepted useful adjunct for the establishment of a positive bacteriological diagnosis. Meunier (1) first used this method in 1898 upon children because of their habit of swallowing their sputum. It was not until 1927, however, that Armand-Debille (2) demonstrated that gastric washings were of value in positively establishing the diagnosis of pulmonary tuberculosis in adults whose sputum had been repeatedly negative for tubercle bacilli.

Roper and Ordway (3) in 1941 demonstrated (1) that the results of a single gastric lavage were insufficient to establish the diagnosis, (2) that usually a series done on consecutive days was necessary, and (3) that an increment in the number of lavages brought an appreciable rise in the percentage of positive results.

Studies made to determine the relative value of culture methods and animal inoculation have proved that all available methods of study should be applied in the search for *M. tuberculosis*. An exception may be made for the direct examination of a smear of gastric washings. In particular, Kayne and Hounslow (4), Roper and Ordway (3), Sasano and associates (5), Robinson and Dunn (6), have shown that simultaneous inoculation of animals and culture media are needed to obtain the highest percentage of positive results, as frequently one will be positive and the other negative. They have pointed out the inaccuracy of direct examination of the gastric smear, how seldom it is positive, and often falsely so. Indeed, Roper and Ordway (3) obtained only 41 smears positive for acid-fast bacilli from 983 patients, 660 of whom had roentgenographic evidence of presumably active tuberculosis. Kayne and Hounslow (4) found that false positive results occurred on direct examination of smears because of contamination of tubes and glassware with acid-fast saprophytes. In addition, there is always the possibility that acid-fast bacilli such as the butter bacillus and Timothy hay bacillus may be in the stomach.

Other experiments have indicated the possible effects of the gastric environment upon the tubercle bacillus. A considerable portion of the bacteriologic diagnosis of tuberculosis in this country is performed in federal and state-financed

<sup>1</sup> From Veterans Administration Hospital 48 and the Communicable Disease Center, U. S. Public Health Service, Atlanta, Georgia.

<sup>2</sup> Published with the permission of the Chief Medical Director, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

laboratories, which receive specimens for study that in some cases may be many hours or even days old. As a consequence, the effects of the gastric secretions on the tubercle bacillus over a prolonged period are important.

Piasecka, Zeyland, and Zeyland (7) of Poland indicated in their work that the saliva of some patients had a marked inhibitory effect upon the tubercle bacillus in culture. Roper and Ordway (3) exposed the tubercle bacillus to normal hydrochloric acid for four days without apparent effect. They also found that free hydrochloric acid in the specimen did not harm the bacillus and that bile had no effect upon it. Floyd and Page (8), however, showed that prolonged exposure to gastric juice itself had an adverse effect upon the cultures of *M. tuberculosis*. In addition, they discovered that duodenal secretion had no such effect. Almost all workers have suggested that the various digestive enzymes may have an injurious effect upon the tubercle bacillus. Moreover, as these enzymes probably require a prescribed hydrogen ion concentration in which to act, the acidity of the stomach has an indirect, but nevertheless potent, effect upon the viability of the bacillus. In a study made to determine the effect of the time element, Sprick and Towey (9) found that a delay of more than 24 hours reduced the percentage of their positive results. Using both animal inoculation and culture methods, they made a 73 per cent positive diagnosis for tubercle bacilli on gastric specimens treated and cultured immediately upon obtaining them from the patient. After a delay of 24 hours, they had only 45 per cent positive findings. With a delay of 48 hours, a positive diagnosis was made in only 21 per cent of the specimens. Their specimens were treated with an equal volume of 4 per cent sodium hydroxide and 0.2 per cent alum immediately, and at 24 and 48 hour intervals, respectively.

Gastric lavage in this hospital is done for two reasons: to establish a positive diagnosis of pulmonary tuberculosis in patients with the typical picture of tuberculosis on chest films, and to evaluate the progress of the patients' disease. This study was undertaken to determine the effect of certain variable factors upon our results, and to study the efficiency of various sized tubes for removal of the gastric contents from the stomach. It is the practice of some European laboratories to use a number 30 French gastric tube, which might be more effective in obtaining the tubercle bacilli from the stomach. The United States Public Health Service Tuberculosis Evaluation Laboratory carried out the culture and animal inoculation work on our first 53 patients. The rationale of the large gastric tube is based on the assumption that the tubercle bacilli are held in the thick mucous secretions of the stomach and that they are also deeply embedded in the rugal folds. The small Levine tube with suction applied does not dislodge these bacilli. With the large tube a large volume of sterile water is introduced rapidly into the stomach with some force. The rugae are washed clean by the force of injection and, when the water is siphoned out, the bore of the tube is large enough to admit large masses of the mucinous material with ease. In addition, it was felt that the introduction of such a large portion of water would dilute the gastric juice to such an extent that the factors which reduce the

viability of the bacilli might be inhibited, whether they be acid, enzyme, or other factors

### TECHNIQUE

The first study consisted of a comparison of the efficiency of the large and the smaller calibre tubes. Each of the first 53 patients, all having repeated negative sputum examinations for tubercle bacilli, had four lavages on successive mornings. The large and small tubes were alternated each day and the lavage was done early in the morning so that often the patients were awakened from sleep for the procedure. The stomach was therefore in a fasting state. Simultaneous 24 hour concentrated sputum specimens were examined during this four day period. In each instance 250 to 300 cc of distilled water were poured down the large tube or injected through the Levine tube with a 30 cc syringe. When utilizing the large calibre tube, the contents were immediately siphoned into a large sterile basin, or not infrequently were vomited by the patient into the basin. Usually 250 to 500 cc of material were obtained. With the use of the small tube, suction was applied at the end of each injection and a smaller total volume, usually 50 to 100 cc, was obtained. It should be made clear that some patients had two or three of these series over a period of months and that four gastric lavages are not regarded as a sufficient number if all studies are negative for tubercle bacilli.

In order to reduce the chances of false positive results, the tubes, syringes, containers, and basins were daily cleaned with soap and water, washed with sodium bicarbonate to dissolve any mucus present, washed with soap and water again, rinsed thoroughly with distilled water, and autoclaved. When the study was begun, it was felt that all patients would prefer the Levine tube because of the smaller size and ease of passage via the nasal route. It was surprising to find that about 55 per cent of the patients preferred the large 30 French gastric tube passed by mouth. It can be passed rapidly with only one cooperative swallow on the part of the patient to get it past the larynx. This procedure is more rapid than with the small tube, but less tidy as the subject not infrequently vomits. One factor became apparent as to the patient's choice of tube. He preferred the tube he did not take first. The first day's experience was more traumatic mentally and physically. Since the first sight of the large tube was so terrifying, most patients "learned" on the small tube and therefore preferred the larger calibre which they received after being "trained."

Once collected, the specimens were treated in the following manner. The specimen was placed in a refrigerator until sediment formed. The supernatant fluid was poured off and the sediment was centrifuged for 15 minutes. Smears were made. If the specimen was thick and mucoid, 10 cc of sodium hydroxide were added, if it was thin, 2 cc of 6 per cent sulfuric acid were added. If sodium hydroxide was used, an inverted rubber stopper was inserted and the specimen was incubated for 20 minutes at 37°C. It was shaken every 5 minutes. The specimen was centrifuged again and the supernatant fluid poured off. If the specimen was treated with sodium hydroxide, two drops of hydrochloric acid were added and it was cultured on four tubes of Jensen's modification of Lowenstein's medium (10). If the specimen was treated with acid (2 cc 6 per cent sulphuric acid), it was left for 10 minutes at room temperature, during which time it was shaken vigorously. Then 10 cc of re-distilled water were added and it was centrifuged as above. The supernatant fluid was poured off and the sediment inoculated directly onto four tubes of the medium. Cultures were kept for 8 weeks at 37°C before being discarded as negative. Young guinea pigs which were injected with 10 cc of the homogenized neutralized specimen inoculated subcutaneously into the groin were autopsied at the end of 6 weeks.

In addition, the specimens from 30 of the 53 patients were divided equally into three parts: one treated and cultured within 4 hours, the others at 24 and 48 hours, respectively. It was believed that in this manner some relationship between the delay and dilution factors might become apparent. It was realized that some inherent error could be present, for Roper and Ordway (3) have shown that, when gastric specimens are divided, some parts are negative while other parts of the same specimens are positive for tubercle bacilli.

## RESULTS

*Direct Examination of Smears*

A careful study was made of the smears from the specimens, a minimum of 30 minutes being spent on the examination of each smear. Of 206 gastric washings from the 53 patients, only 17 smears (14 patients) positive for acid-fast bacilli were obtained. In 6 of the 14 patients, culture and guinea pig inoculation with that particular washing were negative for tubercle bacilli, although 4 of the 6 were found to have positive cultures on a subsequent examination. Therefore, from 206 gastric washings, the presence of acid-fast bacilli on direct examination of the smear was of value in only 2 cases. It is believed that this percentage is too low for the amount of work involved, especially when compared to the possible errors inherent in the direct examination of smears. For example, there was considerable doubt as to the diagnosis of active tuberculosis in these 2 patients with "positive" smears. One was a white man 20 years of age who had had a tuberculous pleural effusion one year previously proved by animal inoculation. Repeated roentgenographic examination of the chest made during the time of this study showed no evidence of activity. Twelve gastric cultures, three guinea pig inoculations and many sputum examinations were negative for tubercle bacilli. The second case was a 23 year old white man who has never had demonstrable tubercle bacilli in the sputum, although he had a cavity which had closed before admission to this hospital. Cultures of 12 gastric washings, a bronchial washing, and many sputum specimens have all been negative for *M. tuberculosis* or fungi. Repeated animal inoculation of similar specimens has also been negative. These patients have been sent to the Veterans Administration Rehabilitation Center as apparently arrested.

In order to examine the possibility of "false positive" smears, each of 12 hospital workers with negative chest roentgenograms were subjected to two gastric lavages. One individual had smears positive for acid-fast bacilli on both occasions, and a specimen from a second individual contained a single suspicious bacillus. Unfortunately, cultures and animal inoculation were not done upon the 2 positive specimens, but a thorough study, including monthly roentgenograms and gastric lavages with proper culture and guinea pig inoculations, have failed to reveal signs of tuberculosis. In the remaining 11 cases, culture and guinea pig inoculation revealed no tubercle bacilli. The possibility of "false positive" smears did not seem remote after this experience.

*Cultures*

In table 1 may be seen that, from the 206 specimens, positive cultures were obtained in 29, or 14 per cent.

Of the 29 positive cultures, 15 were from specimens taken with the large tube, and 14 with the small tube. The number of colonies in each culture was recorded and no conclusions could be drawn in regard to the effectiveness of either tube in relation to the number of colonies per culture. In table 2 the efficiency of the gastric culture in 53 cases is compared with the sputum

examination by the direct smear method. The results are correlated with the stage of the disease as determined by roentgenographic means.

In each series of four gastric lavages only one guinea pig was used. The guinea pig was injected with the first day's specimen only on the day it was obtained. In 6 cases the guinea pigs yielded positive findings where the cultures were negative. In 3, however, cultures on a subsequent day were positive. In the remaining 3 cases, 16 negative cultures and one positive animal inoculation were obtained from four specimens.

There were 9 patients whose specimens were positive for tubercle bacilli on culture although negative on guinea pig inoculation. It should be pointed out,

TABLE 1

*Percentage of Gastric Cultures Positive for M. tuberculosis Based on 206 Specimens*

	TOTAL NUMBER	PER CENT POSITIVE	NUMBER POSITIVE		TOTAL
			Large tube	Small tube	
Specimens	206	14	15	14	29
Patients	53	30	16		16

TABLE 2

*Number of Patients with Gastric Culture Positive for M. tuberculosis Correlated with Roentgenographic Stage of Disease and Subsequent "Positive" Sputum*

	POSITIVE GASTRIC CULTURE, NEGATIVE SPUTUM SMEAR	POSITIVE GASTRIC CULTURE, POSITIVE SPUTUM SMEAR	NEGATIVE GASTRIC CULTURE, POSITIVE SPUTUM SMEAR	NEGATIVE GASTRIC CULTURE, NEGATIVE SPUTUM SMEAR
Minimal	7	5	4	12
Moderate	2	6	0	3
Far advanced	4	6	1	0
Total	13	17	5	15
Cavitation	5	10	1	1

however, that more specimens were cultured than were tested by animal inoculation.

Twenty-two of the 53 patients finally were found to have sputum positive for tubercle bacilli. It is interesting to note that in 11 the bacteriologic diagnosis was established for the first time during the 4 days of gastric washings. Whether or not the tubes cause severe enough coughing to bring up "positive sputum" for the first time is purely conjectural. Most patients found that the large tube caused an irritated throat or pharynx. Two of the "positive" sputum specimens came the day following the bronchoscopy.

A classification of the patients according to the roentgenographic findings

revealed that 11 had far advanced tuberculosis. A positive bacterial diagnosis was made on all of these cases. There were 11 patients whose disease was classified as moderately advanced and of these a positive bacteriologic diagnosis was established in 7. The other 4 had all discharged sputum positive for tubercle bacilli in the past. They were near the end of a long hospital stay and have since been rehabilitated. Of the 28 minimal cases, 13, or 46.4 per cent, were proved positive for *M. tuberculosis* by cultures and guinea pig from gastric washings or by additional sputum studies. Of the 15 patients found to be noninfectious by a series of four gastric washings, only 6 failed to have additional gastric studies. In fact, most had from twelve to fifteen gastric lavages. The 6 patients who received only four washings had stable minimal lesions of many months' duration and had come to this hospital for a periodic review which occupied only a few days. Of the 53 patients, 17 were found to have cavitation, and in 16 a positive bacteriologic diagnosis was established. The one exception was an elderly man with bullous emphysema and no typical inflammatory cavitation. Three of the 53 patients were proved to our satisfaction to have no disease; 2 had an atypical history and negative roentgenographic and bacteriologic studies. The third died of silicosis and postmortem revealed no tuberculosis.

Specimens from 30 patients were divided into 3 portions, one of which was prepared immediately and cultured; the other portions were kept 24 and 48 hours respectively before being cultured. Of these 120 cultures, 11 were positive from those prepared immediately; 6 were positive of those kept 24 hours, and 5 were positive of those kept 48 hours. This series is too small in itself to do more than indicate a trend, but the results were in agreement with the previously quoted observations of Sprick and Towey (9).

Unfortunately, due to shifting personnel, the United States Public Health Service was unable to continue with this program. Our own laboratory was likewise short-handed, and the second 50 patients of necessity were treated in a different manner. These 50 patients each had a series of four consecutive gastric washings, which were treated and prepared for culture immediately as outlined above, but each specimen was kept and combined on the fourth day into one and inoculated upon four tubes of culture medium and into one guinea pig. Necessarily part of each specimen was four days old on inoculation, although they were treated on the day of collection and kept in the ice box. From these 50 patients, 13 specimens were positive for tubercle bacilli on culture or animal inoculation. This represents 26 per cent positive results in contrast to 35.8 per cent positive specimens obtained from the previous 53 patients. Thus, the first method achieved 9.8 per cent more positive results than the second method. In addition to the time element, however, the first method included the use of 16 tubes of culture medium to each patient, in contrast to four for the second method.

#### SUMMARY

Fifty-three consecutive patients whose sputum had been previously negative for tubercle bacilli were subjected to repeated gastric washings, the contents of



their stomachs were collected and studied in various ways in an attempt to find the best method for collection and culture of gastric contents. Studies of the sputum were continued during these tests. An additional group of 50 patients with sputum negative for tubercle bacilli were treated by an abbreviated culture technique and 9.8 per cent fewer positive results were obtained.

### CONCLUSIONS

- 1 The size of the tube used in collecting the specimen is of no consequence.
- 2 The length of time between the collection and the culture of the specimen is of considerable importance. The shorter the time, the greater the chance of success.
- 3 Smears made of the gastric contents are unreliable whether found to be positive or negative for acid-fast bacilli.
- 4 A greater number of positive cases will be found if repeated gastric washings are done.
- 5 Cultures should be made of each gastric lavage immediately and the concentrates of several should not be combined as one.
- 6 Both guinea pig inoculation and cultures should be used in the search for the tubercle bacillus in gastric washings.

### SUMARIO

#### *Valuación de un Método para Obtener Lavados Gástricos*

En 53 enfermos consecutivos cuyo esputo había sido previamente negativo para bacilos tuberculosos, verificáronse lavados gástricos repetidos. Recogióse y estudióse en varias formas el contenido del estómago de los mismos tratando de descubrir la mejor técnica para la colecta y cultivo del contenido gástrico, continuando los estudios del esputo durante dichas pruebas. En otro grupo de 50 enfermos de esputo negativo para bacilos tuberculosos se empleó una técnica cultural abreviada, obteniéndose un 9.8 por ciento menos de resultados positivos.

### CONCLUSIONES

- 1 El tamaño del tubo empleado para recoger el ejemplar no tiene importancia.
- 2 El tiempo transcurrido entre la colecta y el cultivo del ejemplar reviste considerable importancia. Mientras más breve ese tiempo, mayores son las probabilidades de éxito.
- 3 Los frotos preparados del contenido gástrico son poco fidedignos, ya resulten positivos o negativos para bacilos ácidosresistentes.
- 4 El número de casos positivos será mayor si se ejecutan lavados gástricos repetidos.
- 5 Deben hacerse inmediatamente cultivos de cada lavado gástrico, sin combinar en uno solo los concentrados de varios.
- 6 En la busca del bacilo tuberculoso en los lavados gástricos deben emplearse tanto la inoculación en el cobayo como los cultivos.

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# Case Reports

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## **PATHOLOGICAL AND EXPERIMENTAL STUDIES OF BOECK'S SARCOID<sup>1</sup>**

### **1 Report of a Case with Panarteritis, Periarteritis, Terminal-hypertension and Uremia, and the Reproduction of a Sarcoid-like Lesion in Guinea Pigs**

SOL ROY ROSENTHAL

(Received for publication September 7, 1948)

#### **INTRODUCTION**

This is the first of a group of reports that will enlarge upon the thesis of the intimate relationship between sarcoidosis and tuberculosis. Included in these studies is the case report of a patient who was consistently anergic to first and second strength of PPD and was unique in several respects. There was specific involvement of the vessels generally, plus a nonspecific necrotizing arteritis and periarteritis associated with hypertension, uremia, and death. Emulsions of the lymph nodes were negative for tubercle bacilli by smear, culture, and microscopic section. When this material was injected into guinea pigs, however, sarcoid-like lesions were produced in which numerous acid-fast bacilli were found. The microorganisms failed to grow on culturing. The animals responded to tuberculin.

The second report deals with the isolation of banal organisms from autopsy and surgical sarcoid material which had a bactericidal action on tubercle bacilli.

The third report is on a theory of the pathogenesis of sarcoidosis as deduced from further experimental studies in animals and BCG vaccination in two human cases of sarcoidosis.

#### **CASE REPORT<sup>2</sup>**

A colored male, age 22, had been ill for approximately two years. His symptoms began with nosebleeds and headaches, the latter becoming severe. In the first year he lost 30 pounds in weight. What brought him to the hospital eight months before death was chest pain in the right side and a nonproductive cough. He had had paroxysms of fever, chilliness, and night-sweats. On admission he looked chronically and acutely ill. His conjunctivæ were injected and there was marked enlargement of both lacrimal and, to a great extent, the parotid glands. Small soft lymph nodes were noted in anterior and posterior cervical, occipital, and inguinal regions. Both epididymi were enlarged, nodular, and indurated. Many rales were heard throughout the chest. Examination of the ocular fundi showed that the retinal vessels were normal but in the region of the superior nasal vein at the left of the disc there was a linear exudate. A flame-shaped hemorrhage was present in the region of the inferior nasal vein four diopters below the disc. There was general haziness of the cornea and the entire pupillary body of the left eye was drawn in an irregular fashion to the lens capsule. A roentgenogram of the chest showed ill-defined shadows of increased density scattered throughout the lower two-thirds of both lung fields, more marked on the right side. The hilar shadows were considerably enlarged bilaterally. The Mantoux tests with first and second strength PPD were negative as were culture and animal studies of the sputum for tubercle bacilli. Biopsies of three lymph nodes yielded tissue which presented the typical findings of sarcoidosis. Of special interest was the invasion of specific granulomatous

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<sup>1</sup> From Institution for Tuberculosis Research and the Research Foundation of the University of Illinois College of Medicine and the Bruns General Hospital.

<sup>2</sup> Condensed from a summary by Dr. Eric Hausner.

tissue into a medium-sized blood vessel with thrombus-like occlusion of the lumen. The blood count was not remarkable, the total proteins were 6.5 Gm per 100 cc with an A/G ratio of 1.6. Examination of the urine revealed no abnormalities. Roentgenograms of the hands and feet were normal.

#### CLINICAL COURSE AND SUBSEQUENT LABORATORY FINDINGS

The general course was gradually downhill. One month after admission a generalized rash developed, manifested by pinpoint to millet seed-sized, dry, scaly papules corresponding to the sites of hair follicles. The microscopic findings in these papules were compatible with sarcoidosis. These lesions regressed and were not present six months later. The lesions of the epididymi likewise disappeared before those of the skin. Seven months after admission, or one month before death, the patient became confused and would respond only with difficulty. His vision decreased markedly. Multiple irregular masses were palpable in the abdomen. His temperature became slightly elevated and he died twenty-two months after the onset of his complaints. *Tuberculin tests*. On numerous occasions including the last month of the disease the tuberculin tests were persistently negative to the first and second strength of PPD. *Urine*. Four months before his death the urine was normal. Albuminuria with minimal cylindruria and an occasional leukocyte or erythrocyte then appeared. These abnormalities increased to a marked degree. The specific gravity was recorded as being low. *Blood*. A/G ratio remained normal until four months before death, when the serum proteins were 7.1 mg per 100 ml (albumin 2.9, globulin 4.2, A/G ratio 0.69). Three months later the readings were total proteins 7.2, albumin 3.6, globulin 3.6, and an A/G ratio of 1. Retention of nitrogenous products began one month before death, when the readings were nonprotein nitrogen 68, urea nitrogen 54, creatinine 3.9 mg per 100 cc. The carbon dioxide combining power was 22.1 volume per 100 cc and the concentration of chlorides was 429 per 100 cc. The erythrocyte sedimentation rate varied from 100 to 150 mm per hour. The hemoglobin concentration dropped to 13 Gm. The erythrocyte count was 4,300,000, and the total leukocyte count was 8,350 cells per cu mm with a normal differential. *Blood pressure*. On admission, the blood pressure was not remarkable but rose to 160 systolic and 130 diastolic in mm of mercury two months before death. The electrocardiograms were normal except for the presence of a sinus tachycardia. *Roentgenograms*. Repeated films of the chest up until one month of death showed small increased densities which showed evidences of some regression and finally stabilized. *Abdomen*. Flat plates of the abdomen and roentgenographic studies after barium meals were repeatedly negative. Roentgenographic examination of the hands and feet revealed no abnormal findings until three months before death when evidence of periosteal thickening and demineralization was described. One month before death the changes seemed to be less than previously but the proximal one-third of the first metatarsal was definitely involved in the manner described above.

The vitreous of both eyes, but especially of the right, developed many opacities. The final diagnosis was Boeck's sarcoidosis involving the kidneys, lungs, eyes, skin, epididymi, and possibly the small intestine.

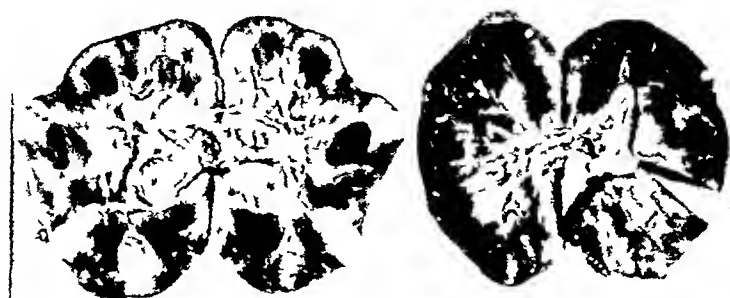
#### POSTMORTEM FINDINGS

The body was emaciated, measuring 69 inches in length and weighing 95 pounds. The only significant external findings were small "shot-like" lymph nodes in the axilla and in the inguinal regions. Small atrophic scars were found over the skin of the arms and legs. There were a few dense fibrous adhesions between the wall of the pleural cavity and the lateral aspect of the right lung.

*Lungs*. The total weight of the lungs was 1,000 Gm. There were scattered fibrous and fibrous exudate over both lungs. Beneath the pleura were pinhead to 6 mm nodules. On palpation, larger nodules were noted as well as fluctuating areas, especially in the upper lobes. The lower lobes contained irregular areas of consolidation. On sectioning, the nodules were gray to black to yellow and granular, or they were composed of small to large thin-

walled cavities up to 2 cm in diameter. In some instances normal lung parenchyma surrounded the nodules, while in others wide zones of red to gray granular areas of consolidation were present. This was especially true in the lower lobes. Some of these cavities extended directly into dilated bronchi.

*Lymph nodes* The hilus, peritracheal, peribronchial, and periaortic nodes were enlarged up to 3 by 2 by 1 cm and on section were mottled gray black. In some of the nodes the cortex was grayish pink and homogeneous with an occasional yellow fleck. The heart weighed 275 Gm and small 3 mm verrucae were present on the free border of the mitral valve, 2



1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23



1 2 3 4 5 6 7 8 9 10

FIG 1 (upper) Both kidneys cut open. Note gray nodular and wedge shaped lesions that involve cortex and medulla. The right kidney is less involved than the left.

FIG 2 (lower) Left kidney. Note nodular masses that disfigure the organ.

mm above the corona. The liver weighed 1,200 Gm and its surface was smooth although studded throughout with milky nodules which were pinhead-sized and grayish white. The sectioned surface was reddish brown with exaggerated markings. The small nodules described beneath the capsule of the liver were present throughout the parenchyma.

The kidneys weighed 250 Gm together (figure 1). The surfaces, especially of the left (figure 2), were deformed by large, tan nodules which extended above the surface and measured up to 4 cm in diameter. The capsule stripped with some difficulty leaving an irregular surface with the nodules already described. In the center of some of these nodules were irregular areas of light yellow. The nodules described on the surface extended throughout

the entire parenchyma and measured up to 2.5 cm. in width and 1.5 in depth, in some instances they were wedge shaped. The architecture of the parenchyma was otherwise discernible although there was diffuse purple yellow and red mottling. The pelvis was not dilated and the mucosa was pale. The peripelvic fat was serous in nature. The prostate and seminal vesicles were essentially normal. The testicles together weighed 30 Gm. The epididym were diffusely indurated and slightly nodular. On section they appeared to be transformed into dense fibrous connective tissue in which small islands of a lighter tan were noted. There was no evidence of cystitation or granulomatous gross examination. The tunica vaginalis and tunica albuginea appeared markedly thickened. The testicle proper was discolored a yellow tan in which numerous fibrous strands were noted. The seminiferous tubules did not separate easily.

*Brain and cervical cord.* Except for some edema the pons and rhomboid was grossly not remarkable. Both eyes were removed and sent to the Army Medical Museum. The report will appear in another publication.

#### HISTOLOGY

*Lungs.* Scattered throughout the section were discrete nodules composed of epithelioid cells and occasional multinucleated giant cells. There was no reaction about these nodules. The cavities described in the central portions of the pneumonic areas were lined by dense fibrous connective tissue although it was very narrow in places. At such points dilated vessels as well as alveoli encroached very close to the lumen. In the smaller cavities, bronchial epithelium, high columnar in character, for the most part denuded, were noted. In some areas of the wall there were broad zones, easily occupying an entire low power field in which only hyalinized connective tissue was found with an occasional large giant cell of the foreign body type, swollen histiocytes, and round cells. There was also a proliferation of bronchial epithelium to form pseudoglandular areas. Occasionally such a structure was filled with fibrin and pus cells. Broad bands of fibrous connective tissue were found throughout the section in which an occasional epithelioid cell and giant cell could be found. The intervening lung parenchyma was composed of alveoli which were packed with pus cells and fibrin. One could still discern dilated atria and alveoli suggestive of an emphysema. The pleura was markedly thickened and was fused with some of the focal areas of fibrous connective tissue of the lung parenchyma. Here, too, one found a giant cell of the Toulon or even the Laughlin's type in addition to the foreign body variety. Elastica Van Gieson stain revealed that the hyalinized fibrous connective tissue was dispersed through the lung parenchyma as focal nodules as well as connecting bands, all staining red to reddish pink. The walls of the cavities were lined by dense fibrous connective tissue for only approximately one third of their diameters, the remainder being composed of delicate fibrils staining reddish pink. A striking feature was the paucity of elastic fibrils in the alveolar walls. One noted small fragments of black staining fibrils on only one aspect of an alveolar wall or none at all. The dilated bronchi with intact epithelium described contained only an occasional elastic fibril. Many of the veins presented a thickening of the internal elastic membrane with proliferation of fibrils as well as interruption of the internal elastic membrane. In some the intima was wide as a result of connective tissue proliferation.

*Hilus and peritracheal lymph nodes.* Despite the fact that 90 per cent of the lymph node was involved in the granulomatous process, the marginal sinuses were wide and showed practically no involvement. The normal architecture of the node had been entirely disrupted. Both cortex and medulla were the seat of fibrosis and hyalinization in which an occasional giant cell and groups of epithelioid cells were found. Occasionally there were typical granulomas composed of an epithelioidfibrocyte type of cell as well as an occasional giant cell. Silver stain revealed an intricate network of argentophil fibrils extending throughout the entire gland showing only rare dissolution within some of the active granulomas. Some of the giant cells presented inclusions composed of irregular deep blue staining bodies (hematoxylin and eosin stain), the so called Schaumann inclusion bodies. Other giant cells contained vacuoles or phagocytized nuclear debris. On examination of five left axillary

nodes, the involvement could be traced from a single healed nodule in the center of a follicle up to 50 per cent involvement of the node. In every case the specific granulomas were found in the center of the follicle and never in the marginal sinuses. Stages were noted from the epithelioid tubercle through those with fibrinoid central necrosis and finally to those showing hyalinized scarring. Silver stain revealed only slight dissolution of the argentophil fibrils, especially in the region of specific granulomas. Crystal violet stain was negative for amyloid.

There was no specific involvement of the heart, spleen, pancreas, or gastro intestinal tract.

*Liver* Scattered throughout the liver were milium nodules composed mainly of a coagulation necrotic material in which nuclear debris was still in evidence with a small peripheral zone of fibrocytes, occasional giant cells, and a zone of lymphocytes. The liver cords otherwise were fairly well preserved. The capillary sinuses were wide and there was an increase in periportal connective tissue. Sudan II stain revealed a diffuse deposit of lipid material in the liver cells as well as in the central portion of the tubercles described.

*Kidneys* The larger nodules described grossly were composed of coagulation necrotic material in which ghosts of the original structure were still discernible. This was even more clearly demonstrated by the Elastic Van Gieson stain. There were no specific or round cell infiltrations about the necrotic zone but capillary dilation was prominent. The necrotic foci blended in with the kidney parenchyma although there was a marked interstitial fibrosis adjoining the nodules. In addition to these large areas, there were smaller foci composed of epithelioid cells which sometimes showed central fibrinoid necrosis and contained a rare giant cell. In other places such nodules were composed of hyalinized connective tissue only. A striking feature was the involvement of the medium-sized and smaller arteries. The medium-sized arteries, especially in the medulla were surrounded by and invaded with a granulation tissue that was composed of fibrous connective tissue for the main part, histiocytes, and an occasional epithelioid and giant cell. Many of the vessels were almost completely occluded by such well-organized thrombi. Sections of the wall of the artery were entirely replaced by a similar pathology which interrupted the elastic and muscle tissue bundles. Many of the small arteries of the cortex were surrounded by epithelioid cells, giant cells, and a few round cells, media and adventitia were nuclear while the intima still maintained an intact endothelium (figure 3). Other vessel walls were entirely anuclear as well as the surrounding tissue for distances of three and four times the width of the vessels (figure 4). There was no cellular reaction of any kind. The walls were edematous and stained diffusely pale pink with hematoxylin and eosin. Still other medium-sized vessels were completely obliterated by dense fibrous connective tissue in which recanalization was present or absent. Elastic Van Gieson stain revealed in such instances an interruption of the internal elastic membranes with marked proliferative changes in the intima to complete occlusion (figure 5). Other changes consisted of dilatation and atrophy of the convoluted tubules in which numerous casts were noted. There was marked interstitial fibrosis and a certain amount of thickening of the afferent arterioles to the glomeruli. Some of the glomeruli showed atrophy and hyalinization of the glomerulus proper. The medulla was relatively uninvolved. The pelvis showed a slight amount of round cell infiltration beneath the epithelium but this was not excessive. Fat stain revealed that the central portion of some of the large necrotic areas contained much fat and that numerous phagocytes also laden with fat surrounded such areas, a fact not clearly evident with the hematoxylin and eosin stain. There also appeared to be fat in the glomerular capillaries, being present in the lumen of some of these vessels as well as in the endothelium. Many of the casts took the fat stain. The epithelium of the tubuli showed very little fat.

No definite abnormalities were noted in the prostate. In the epididymis there was an increase in fibrous connective tissue which in places effaced some of the ducts. In addition, there were accumulations of round cells in which swollen epithelioid cells were noted. Although these infiltrations were not characteristic of a specific involvement they were very suggestive of transformed specific nodules by secondary round cell infiltration.

*Testicle* The tunica vaginalis was markedly thickened by dense fibrous connective tissue in which small granulomas were scattered, composed of epithelioid cells and round cells. An occasional giant cell was noted. The vessels showed no specific involvement. There was a marked increase in fibrous connective tissue within the testicle proper with reduction of the number of interstitial cells. Spermatogenesis was not noted and there were no spermatozoa in the lumen of the tubules.

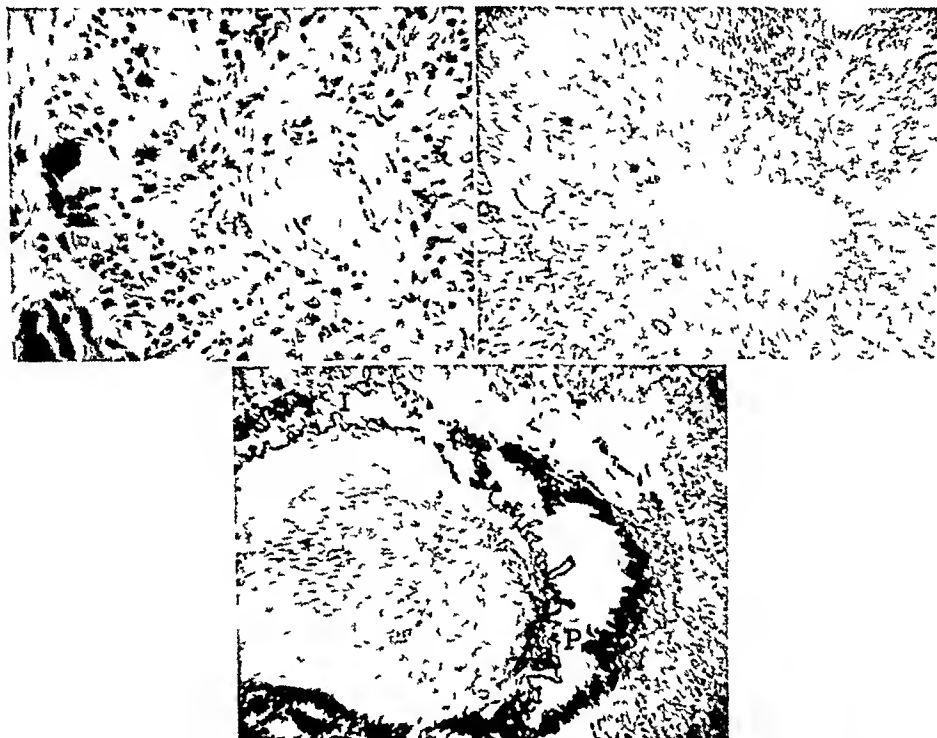


FIG 3 (upper left) Specific granulomatous periarteritis and arteritis of small artery of kidney. Note typical sarcoid granuloma about vessel and edematous vessel wall with some cellular infiltration.

FIG 4 (upper right) Nonspecific necrotizing arteritis and periarteritis. Note edematous anuclear wall of small artery and almost complete occlusion of lumen. The kidney parenchyma about vessel is also anuclear.

FIG 5 (lower) Complete obliteration of lumen of medium sized artery of kidney. Occasional giant and epithelioid cells are still present in the fibrous tissue thrombus. Note interruption of elastic membranes at various points (I) and proliferation of same at others (P). Elastic Van Gieson stain. This vascular change resembles the surgical biopsy of lymph node taken eight months before death except that the thrombus was more granulomatous.

*Pituitary* There appeared to be small foci where the cellular elements showed varying stages of degeneration from swelling of the cells and hyalinization thereof to pyknosis and disintegration. Basophilic cells were prominent but they did not supersede the eosinophilic variety. The pars nervosa was not remarkable.

*Skin* The architecture was well preserved. There was no specific process in the sections studied or noticeable vascular changes.

*Brain* (Frontal, occipital lobes, internal capsule pons) The piaarachnoid over the occipital lobe was infiltrated with histiocytes and round cells. Scattered throughout the brain were solitary nodules composed of either a central giant cell or capillary and surrounded by



exudate of epithelioid fibroid type of cells. In some instances, the central vessel was obliterated by similar exudate. In the medulla, the Virchow Robin space about small vessels were surrounded by cuffs of histiocytes, round cells, pus cells, plus a small zone of necrosis eccentrically located. This exudate extended into the wall of the vessel, at times obliterating the lumen. The parenchyma surrounding the vessel was also involved with a similar exudate. Fat stain revealed a yellow staining material in some of the capillaries of the cortex free in the lumen as well as in the endothelium of the capillaries. No fat was found about the capillaries, free or within so called gutter cells.

*Cervical cord*—A small nodule was noted in the commissure composed of a central coagulation necrotic zone and periphery of swollen histiocytes and round cells. Some of the vessels showed cuffing with a hyaline degeneration of the vessel wall and narrowing of the lumen (figure 6). This was found in both gray and white matter.

There was a pale pinkish blue (hematoxylin and eosin) matrix scattered throughout the bone marrow, arranged in irregular alveoli suggestive of the old fat spaces. Fat was practically absent. There was marked myelopoiesis but the shift was decidedly to the right. Erythropoiesis was rare, the relation being about 10:1. There were peculiar giant cells,

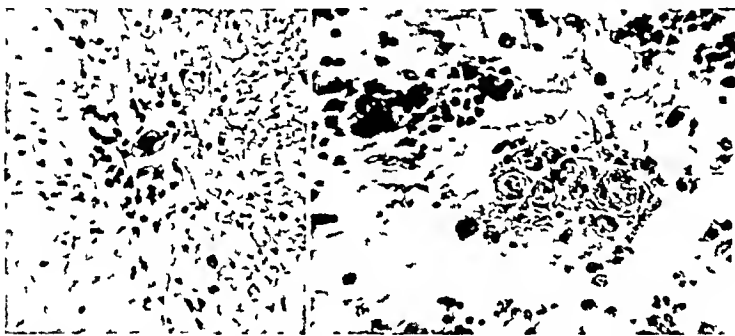


FIG 6 (left) Cervical cord with perivascular cuffing and hyaline degeneration of vessel wall and marked narrowing of lumen.

FIG 7 (right) Bone marrow showing small arteries with thickened walls and narrowed lumina.

some containing bizarre nuclei with pyknotic chromatin, others were multinucleated and resembled a foreign body type, yet there were no definite granuloma of a specific process. Vascular changes were prominent in that small arteries showed marked narrowing of their lumina as a result of internal proliferation, the lumen to wall ratio being 1:4 (figure 7). *First metatarsal bones* (Head, left and right). On gross inspection of the slide, one immediately noted that the left was more delicate in its architecture than the right. The articular cartilage of the left was one-half to one-third the thickness of that on the right. An enchondral zone of calcification was distinct but narrow. The bony trabeculae were about one-half to one-third the thickness of those on the right. The periosteum of the left, however, was greatly thickened as compared to the right, in places being two to three times as thick and composed mainly of what appeared to be a hyalinized connective tissue. The bone marrow in both was fatty and showed very little response. The larger vessels present in the section of the left showed thickened walls, some as a result of hyperplasia of the intima. The lumen to wall ratio at times was 1:1 on both sections. No specific process was noted in left or right metatarsal bones.

#### *Bacteriological Studies*

Ziehl-Neelsen stain of smears from the lung and sections of lung, kidney, liver, spleen, and lymph nodes revealed no acid-fast bacilli. Methylene blue and MacCallum's stains

for bacteria revealed bizarre gram-negative bodies in some of the cells of the reticulo-endothelial system, especially of the lymph nodes, but the identity of these bodies was not certain. Cultures from the unconcentrated hilus lymph nodes on egg media were negative for tubercle bacilli after twelve weeks of observation. Culture of the lung after concentration in 4 per cent sodium hydroxide and neutralized with 15 per cent hydrochloric acid was negative for tubercle bacilli after twelve weeks. Emulsions of the hilus lymph nodes were cultured on blood agar, brain infusion broth, and endos media. A number of banal type of organisms were isolated, the identity of which shall be discussed in a subsequent paper.

#### *Animal Inoculations*

Emulsions made of the hilus lymph nodes were injected in 0.1 ml. amounts in 8 different skin sites of 2 guinea pigs. Another 2 guinea pigs were inoculated with 1.0 ml. of the emulsions intraperitoneally. The animals were tuberculin tested with 10 mg. of O.T. at intervals of three to six weeks. These reactions were strongly positive in all animals at both testings. Skin biopsies were taken at weekly intervals for three weeks and then again at six weeks. The lesions of the skin developed slowly and at three weeks varied in size from .5 to 1.0 cm. but regressed to some extent although not completely six weeks after the inoculation. The animals died of enteritis which was present in many of the noninjected animals as well. Microscopic sections of the skin biopsies revealed a nonspecific inflammatory type of reaction with pus cells and histiocytes but no giant cells.

#### *Postmortem Examination of the Animals*

*Intradermally inoculated group:* The lymph nodes draining the skin near the site of inoculation were enlarged, contained gray yellow nodules that were firm but were not caseous. The liver and spleen were enlarged showing an occasional yellow gray nodule up to 3 mm. in diameter. The lung and hilus lymph nodes were not remarkable.

*Microscopic examination (guinea pig 45-24):* There were small foci of necrosis, without cellular response in the liver. However, there were specific nodules with central coagulation necrosis and epithelioid cells surrounding it in which an occasional round cell was scattered (figure 8a). The spleen was studded by numerous nodules, discrete and confluent, of epithelioid cells in which an occasional giant cell was noted. No reaction about these nodules was found. About 50 to 75 per cent of a lymph node situated at the crest of the ilium (figure 8b) was replaced by a specific process composed mainly of histiocytes arranged in nodules either discrete or confluent. An occasional giant cell was noted (figures 9a, b). There was no specific involvement of the kidney. A suspicious nodule composed of epithelioid cells and round cells with a suspicious giant cell was found surrounding a capillary in the lung (figure 8c). Fifty per cent of the peritracheal lymph nodes was replaced by a specific process composed of epithelioid cells with few other types of cells. Giant cells were rare. Reactive phenomena were practically absent. Deep in the cutis was a perivascular accumulation of round cells and histiocytes, nonspecific in character. There was no specific involvement of the pancreas but a peripancreatic lymph node was replaced to the extent of 75 per cent of a specific process composed of discrete and confluent nodules, some showing marked central fibrinoid necrosis in which nuclear debris was prominent. Giant cells were scarce. There was a marked epithelioid reaction and very little response about the nodule. Ziehl-Neelsen stain revealed acid-fast bacilli in liver, spleen, all lymph nodes, and lung.

*Microscopic examination (guinea pig 45-22):* The nodules in the spleen had central coagulation necrotic areas in which there was cellular debris and were surrounded by an epithelioid-like reaction in which granulocytes and lymphocytes were also intermingled. In the liver there were discrete nodules composed of centrally degenerated areas surrounded by epithelioid cells, granulocytes, and lymphocytes. Some of the areas presented calcifica-

tion centrally. No remarkable changes, vascular or otherwise, were noted in the kidney. Scattered throughout the cortex of the peritracheal lymph nodes were discrete and con-

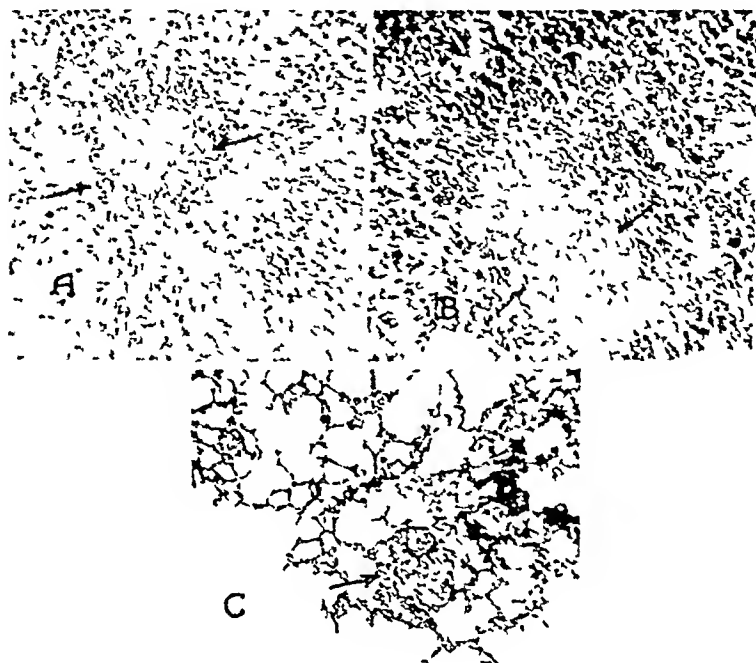


FIG. 8. Guinea pig (nutrient meiosis group). Miliary nodules of liver (A), spleen (B), and lung (C). The lesions are composed mainly of swollen histiocytes and an occasional giant cell. Note absence of reaction about the nodules.



FIG. 9a. Section of entire lymph node of guinea pig. Note diffuse involvement of about one third of cortex and medulla (D) and miliary nodules (N) in remainder of node. All marked lesions are from pathology.

FIG. 9b. High power. Nodule granulomatous lesion composed of swollen histiocytes, foamy macrophages, and central giant cell.

centric nodules composed of epithelioid cells. Each nodule peripheral to the center. As a result, the nodules are surrounded by a thin layer of epithelioid cells. The nodules are composed of epithelioid cells and central giant cells. The nodules are

vade the cortical sinuses which were free. Some of the nodules had accumulations of pus cells centrally, many of which were degenerated. The position of the lesions and the nature of the reaction, except for pus cells, simulated very closely those found in the lymph nodes of the patient. Examination of two sections of the lungs failed to reveal any specific changes. Ziehl-Neelsen stain revealed acid-fast organism in the spleen and peritracheal lymph nodes.

Only one of the animals inoculated intraperitoneally was examined post mortem. The spleen was slightly enlarged and presented occasional yellow gray nodules without evidence of gross caseation. There were no other remarkable findings.

*Microscopic examination (guinea pig 45-23)* There were several nodules in the spleen which were confluent, composed of epithelioid cells for the most part in which an occasional round cell and giant cell was dispersed. One of the nodules had a central area suggestive of coagulation necrosis. In the peritracheal lymph nodes there were small zones, especially in the cortex, composed of epithelioid cells which did not form distinct nodules. There were no specific changes in the lung or liver. Ziehl-Neelsen stain revealed acid-fast organism in the spleen.

Lesions of the organs of each animal were pooled, emulsified, and concentrated (4 per cent sodium hydroxide neutralized with 15 per cent hydrochloric acid) and spread over egg media. No growth occurred after six weeks of incubation.

#### *Anatomical Diagnosis*

- 1 Sarcoidosis, generalized, involving lungs, kidneys, liver, peritracheal, peribronchial, and hilus lymph nodes, and brain and meninges
- 2 Panarteritis and periarteritis of small and medium-sized arteries, generalized, sarcoid, and nonspecific in character
- 3 Emboli, fat, of glomeruli and capillaries of brain
- 4 Infarcts, ischemic, of both kidneys
- 5 Encephalitis, disseminated, and myelitis
- 6 Osteoporosis of first metatarsal and thickening of periosteum, left
- 7 Bronchiectasis, focal, saccular, with cyst formation, of both lungs
- 8 Bronchopneumonia of entire lung and lower lobe of left lung
- 9 Atrophy, fibrotic, of spleen
- 10 Atrophy and fibrosis of both epididymides and testicles

#### DISCUSSION

This typical case of sarcoid, in which the tuberculin test remained negative throughout, presented almost every form of disease heretofore described plus renal manifestations which were hitherto unreported. Thus, there were syndromes related to the eyes, parotid glands, skin, bone, central nervous system, and milary involvement of virtually every organ in the body. The lesions of the kidneys were primarily vascular, with specific granuloma surrounding and/or invading the medium-sized and small arteries, occluding some to a marked degree (panarteritis and periarteritis). These vascular occlusions led to infarcted areas of necrosis of the parenchyma of the kidney. In addition to the specific changes, there were nonspecific alterations of the small arteries that appeared to be more recent. There was diffuse necrosis of the entire wall which in some instances extended to the perivascular tissue. Vascular changes were present in other parts of the body. The small arteries of the central nervous system were for the main part surrounded by round cells, some having edematous walls, others showing complete necrosis of the walls. The bone marrow and epididymis presented thickened walls and narrowed lumina of small arteries. The small arteries leading to the lymph nodes presented invasion by specific granuloma, with occlusions of their lumina. Involvement of the kidney by milary sarcoid nodules has been described frequently, but clinical symptoms related to the kidneys in sarcoidosis have been rare. Azotemia has been reported in 4 cases with nonprotein nitrogen values up to 90

mg per 100 cc (1, 2, 3, 4) These findings were not associated as a rule with an elevation of the blood pressure (154 systolic and 115 diastolic in one case) (3) The urines in these cases had a low specific gravity (1.006 to 1.012) with albumin and casts Only one of these cases came to autopsy (2) The kidneys were somewhat smaller than normal with a granular surface Miliary sarcoid nodules as well as caseating nodules of tuberculosis were found on microscopic examination In the case here reported the terminal picture was that of a malignant hypertension with uremia The highest nonprotein nitrogen (post mortem) was 360 mg and the creatinine 4.5 mg per 100 cc The etiology of the hypertension can be ascribed to the occlusion of the medium-sized arteries by specific sarcoid granuloma, simulating the Goldblatt type of kidney The occlusion of the arteries, however, was complete in many instances and resulted in multiple anemic infarcts The nonspecific thickening of the walls of the small arteries associated with the narrowing of the lumina, as noted in other parts of the body (bone, marrow, epicardium, epididym), is probably related to the hypertension The necrosis of the walls of the small arteries in the kidneys as well as in other organs appeared to be a more recent process as it was not observed in the nodes removed surgically eight months before death of the patient At that time there was specific granulomatous involvement of the arteries It is difficult to determine whether or not the necrotizing arteritis was related to the hypertension, the sarcoid specifically (5), or to a terminal hyperergic state (6) Necrotizing arteritis has been described in all three conditions Staehlen (5) reported necrotizing arteritis and periarteritis nodosa in a case in which the sarcoid-like pathology originated in the nose, extended directly to the brain, and finally metastasized to the rest of the organs Similar findings were observed by Weinberg and Gartside (8), Rossie (9), and Teilum (10) The cyst-like cavities of the lungs here described were mentioned in only two reports (11, 12) Rubin and Pinner (11) considered the process to be on an emphysematous basis The studies here presented using special connective tissue stains indicate that it is bronchiectatic in character resulting from peribronchial fibrosis and loss of elastic tissue The absence of involvement of the afferent lymph channels and the marginal sinuses by the granulomatous process in the vast majority of the lymph nodes studied in this case makes this feature an aid in the differential diagnosis of sarcoidosis and tuberculosis Except in miliary tuberculosis of the lymph nodes, invasion of the nodes is usually by way of the lymphatics with tubercles in the marginal sinuses In sarcoid this is rare, as the disease in the nodes is most likely on a hematogenous basis In examining many surgical specimens this fact was borne out Rarely there may be extension of the cortical process into the marginal sinuses The significance of Sudan III staining material in the capillaries of the glomeruli and in the endothelium proper, as well as in the lumen and the endothelium of the brain capillaries, and the near depletion of fat in the bone marrow sections studied is not completely understood This subject will be discussed in a subsequent paper where experimental studies in animals gave a possible clue

The most unusual findings were the lesions in the guinea pigs injected intradermally and intraperitoneally with an emulsion of the hilar lymph nodes Weekly biopsies of the skin of the former for three weeks and one at six weeks showed no specific pathology but the lesions persisted for six weeks The tuberculin test was strongly positive in both groups of animals after three and six weeks using 10 mg O.T. Upon the death of the animals six weeks after inoculation, gross and microscopic lesions of the lymph nodes, liver, spleen, and lung were suggestive of sarcoidosis This was especially true of the intradermally injected animals Here, as in humans, the involvement of the lymph nodes excluded the marginal sinuses Ziehl-Neelsen stains revealed numerous acid-fast bacilli in the liver,

spleen, lung, and lymph nodes. Cultures of these organs on egg media were negative for tubercle bacilli. The hilar node of the patient was used for the inoculation because it was one that was extensively involved and was large enough to serve for entire experiment of cultures, smears, and animal inoculations. There was no evidence of tuberculosis in this node as noted by microscopic section, smears, and numerous cultures of the digested and undigested material. Search for the tubercle bacilli in the human material whether by microscopic section, smears, or cultures was entirely negative. Cultures of the lymph nodes on brain infusion broth, blood agar, and thioglycolate media did yield a group of banal type of organisms which shall be discussed in a later paper. In the histologic sections, unidentified gram-negative bodies were found in the cells of the reticulo-endothelial system of the lymph nodes by methylene blue and MacCallum's stains for bacteria.

#### SUMMARY

1 A case of Boeck's sarcoid is described with the unusual features of generalized specific arteritis and periarteritis as well as nonspecific necrotizing arteritis. Associated with the above were hypertension and uremia.

2 Sarcoid material injected intradermally and intraperitoneally into guinea pigs produced a hyperergy to Old Tuberculin and lesions of the lung, liver, spleen, and lymph nodes that closely resembled sarcoidosis. Numerous acid-fast bacilli were found in the lesions but cultures of the organs were negative for tubercle bacilli.

3 A banal group of organisms was isolated from human sarcoid material and will be elaborated upon in a later report.

#### SUMARIO

*Estudios Patológicos y Experimentales del Sarcoides de Boeck. Comunicación de un Caso con Panarteritis, Periarteritis e Hipertensión y Uremia Terminales, y Reproducción de una Lesión Sarcoides en Cobayos*

1 El caso de sarcoides de Boeck descrito mostraba las características extrañas de arteritis y periarteritis específicas generalizadas así como de arteritis necrosante inespecífica, habiendo además hipertensión y uremia.

2 La sustancia sarcoides inyectada intradérmica e intraperitonealmente en cobayos produjo hiperergia a la tuberculina antigua y lesiones de los pulmones, hígado, bazo y ganglios linfáticos, muy semejantes a sarcoidosis. Aunque se encontraron numerosos bacilos tuberculosos en las lesiones, los cultivos de dichos órganos fueron negativos para dichos bacilos.

3 Del material sarcoides humano se aisló un grupo de microbios banales que se comentará más a fondo en un informe subsiguiente.

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## ERYTHEMA INDURATUM BAZIN<sup>1</sup>

Report of a Proved Case Associated with Tuberculous Lymphadenitis, Completely Relieved by Tuberculin Desensitization

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### INTRODUCTION

The literature on the subject of erythema induratum has been rather scant in recent years. It consists mainly of brief remarks dealing with clinical diagnostic features in transactions of dermatological societies, with only an occasional mention of unsuccessful therapy. The internist, apparently, is little acquainted with this entity, notwithstanding the fact that erythema induratum is merely a reflection of a systemic disease process.

The purpose of this report is to consider some etiologic and pathologic factors of Bazin's disease and to demonstrate the feasibility of a therapeutic success by means of desensitization with Old Tuberculin, for some reason a forgotten therapeutic agent.

Comparatively little has been added to the original description of erythema induratum by Bazin (1) in 1861. He pointed out that the red indurated plaques are prone to develop in girls of scrofulous constitution, that they appear commonly on the legs, although they might occasionally occur elsewhere, that these plaques are never itchy and seldom tender. These clinical features, however, are apparently insufficient for diagnosis by themselves, as there are other nontuberculous conditions which may give rise to nodular erythematous lesions within the skin and subcutis with which erythema induratum might easily be confused, e.g., erythema nodosum (2). Moreover, Montgomery and his associates (3) pointed out that somewhat similar lesions clinically may also develop on the basis of vasculitis and that still others, previously reported as instances of erythema induratum, are more properly classed with the so-called sarcoid lesions of the skin. Obviously, an accurate diagnosis is essential for a fair therapeutic evaluation. It is particularly important when the therapeutic aim lies further than the local expression of the disease, and the therapeutic agent requires considerable caution in its administration.

### REPORT OF CASE

*First admission.* The patient, a 35-year-old former Viennese dancer, was admitted to this hospital for the first time on October 3, 1939, complaining of painful red nodes on her legs associated with swelling of the ankles, and also of some lower abdominal pain. She stated that she had had "ovarian trouble" since the age of 19, with exacerbations from time to time. She had also had leukorrhea for many years. In 1931 she had "dry pleurisy." During the year prior to admission, she had lost five pounds in weight. The menstrual cycle was normal. The history was not significant otherwise.

The lesions on her legs, which constituted the major complaint, had first appeared in 1929 as erythematous, hard, tender lumps about both ankles. At that time, tonsillectomy was done and the patient also received some heat treatment. The lesions, however, persisted some months after the tonsillectomy and then regressed spontaneously, although the patient claimed that she was "always sick with her legs" during this period. The lesions again recurred in 1932, lasted several months, and again disappeared spontaneously. She had two more recurrences of the same difficulty in 1936 and in 1937, for which she received

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biking and mud treatment in Carlsbad. Each time the lesions lasted several months in spite of therapy, and then regressed. The most recent recurrence, for which she was admitted to this hospital, took place in August 1939. With each crop of tender nodes on her lower legs, swelling about the ankles appeared, especially during activity. It should be noted that the occurrence of the lesions was not related to the menstrual cycle and was apparently independent also of the season of the year.

*Physical examination.* The eyes, including the fundi, were negative. The upper teeth were replaced by a plate, the lower gums were tender. Examination of the heart and lungs revealed nothing abnormal. The blood pressure in mm. of mercury was 95 systolic and 60 diastolic. Palpation of the abdomen revealed slight tenderness in both lower quadrants and on pelvic examination there was noted a diffuse tender induration, the size of a fist,



FIG. 1. Photographs showing the presence of multiple indurated nodes on the posterior and lateral surfaces of both legs. These nodes were tender and many of them, though not all, were erythematous. Some swelling of the ankle regions was also present.

situated to the right of the midline and limiting the mobility of the uterus. Neurologic examination was negative except for absence of the left knee jerk. On the posterior and lateral surfaces mainly of both legs, there were a number of erythematous areas, varying in size from 1 to 2 cm. in diameter and, beneath them, tender indurated nodes were palpable. Nodular indurations could also be felt in other areas on the calves, where the overlying skin was not erythematous. Some edema of the ankles was present (figure 1). Aside from the legs, only a single nodule on the lateral surface of the right arm was observed.

The laboratory findings were not significant except for an increased sedimentation rate, varying between 13 and 50 mm. in 45 minutes. The Kahn and Kline tests were negative. A smear of the cervix was negative. Roentgen examination of the chest failed to show any evidence of old or recent tuberculosis. Roentgenograms of the bones of the lower extremities were negative. The tuberculin test was positive in dilution of 1:10,000, but was negative in higher dilution.

During the patient's stay in the hospital, the temperature remained below 100° F. On

the tenth hospital day, the patient presented two white centered papular lesions on the left index finger which later became purplish ind, subsequently, wart-like in appearance. The patient recalled having had such lesions previously on her palms. After several days, the lesions on the lower extremities became purpl, less indurated, and somewhat scaly, and the tenderness abated. However, there was a tendency for new lesions to appear. At about this time also an eruption of small red papules appeared on the right buttock. While in the hospital the patient received twenty short wave treatments to the pelvis, and was discharged on November 10, 1939. A tentative clinical diagnosis of erythema induratum was made by one of us (T T I), although some observers leaned toward the impression of erythema nodosum. It was felt also that the erythematous skin lesions were somehow associated with the pelvic condition.

*Second admission* (November 21, 1939 to February 10, 1940) The second admission was prompted by the appearance of a painful nodule above the medial portion of the left clavicle and the recurrence of a fresh crop of tender indurated nodules, many of them erythematous, on the upper, as well as on the lower, extremities, including one on a finger. Examination revealed a group of tender, enlarged supraclavicular lymph nodes. The chest was clear. The patient was again afebrile. From time to time, additional small, firm, tender, subcutaneous plaques appeared on the limbs and tended to regress after 12 to 48 hours. The tuberculin test was repeated and found definitely positive in dilution of 1:10,000, slightly positive in dilution of 1:100,000, but negative in higher dilution.

*First skin biopsy* On December 7, 1939, a biopsy of a nodule on the right leg was done. The specimen consisted of a small piece of skin and a few bits of subcutaneous fat tissue. Sections of the cutis showed slight keratosis, subpapillary fibrosis, and perivascular infiltration with lymphocytes, mononuclear cells, and an occasional polymuclear leukocyte. More significant changes were observed in the subcutaneous fat tissue. Within the latter, there were numerous focal, discrete, or conglomerate nodules composed largely of epithelioid-like cells and infiltrated by lymphocytes, scattered polymorphonuclear leukocytes, and a number of eosinophils. Some of these nodular foci contained small giant cells. A few of them presented suggestive areas of necrosis. While they had some resemblance to tubercles, their morphology was by no means typical. The adjacent fatty tissue showed fibrosis and infiltration by inflammatory cells. No vascular lesions of any kind were observed. By way of diagnosis, it was stated at the time that the findings were not those generally associated with erythema nodosum. While the specific diagnosis of erythema induratum was not made, the opinion was expressed that the condition might conceivably represent some peculiar expression of tuberculous reaction within the subcutaneous fat tissue (figure 2).

*First lymph node biopsy* On December 20, 1939, an enlarged lymph node from the left supraclavicular region was removed for biopsy. At the same time some of the pertinent tissue was used for guinea pig inoculation. The guinea pig was sacrificed after ten weeks and showed no evidence of tuberculosis. Sections of the lymph node showed its architecture to be completely altered and replaced by a pleomorphic cellular tissue rich in fibroblasts. Dispersed within this tissue were numerous cells, apparently of reticulum cell origin, with peculiar large oval nuclei and large eosinophilic nucleoli. Many of these cells were multinuclear. The histologic picture presented by this lymph node was regarded as being very suggestive of Hodgkin's disease (figure 4A).

*Second skin biopsy* On February 1, 1940, a biopsy was again taken of a subcutaneous nodule on the left leg. The specimen consisted of several small bits of somewhat indurated, subcutaneous, fat tissue. These showed merely a few focal collections of chronic inflammatory cells, principally around the smaller blood vessels.

While in the hospital, the patient received several roentgen treatments over the lower extremities without apparent benefit, and she was referred to the Outpatient Department for further observation. In the course of the next several months, she received additional X-ray therapy directed against the constantly recurring lesions on the lower extremities without demonstrable effects, and the administration of liver extract and vitamin preparations was likewise ineffectual.

*Third admission* (October 15, 1940 to November 15, 1940) The patient again returned,

presenting on the extensor surfaces of both calves numerous red, warm, tender areas which were indurated and raised above the surface of the skin. A few similar lesions were present also on the thighs. There was a coalescence of these areas about the ankles, with general induration but no edema. On the arms, a few irregular subcutaneous plaques were palpable, and over both elbows there were reddened, glistening papular, circular lesions, which were psoriasis like in character. It was thought by some observers that the spleen was enlarged. The laboratory findings were essentially as previously recorded.

*Third skin biopsy.* Still another biopsy of a nodule on the left leg was taken on November 2, 1940. The specimen consisted of several bits of subcutaneous fat tissues, one of which was covered over by a strip of skin. The fat tissue was somewhat indurated and in places presented a number of grossly discernible, small, yellowish, milium nodules. Microscopic sections showed essentially the same findings that were observed in the previous biopsy.

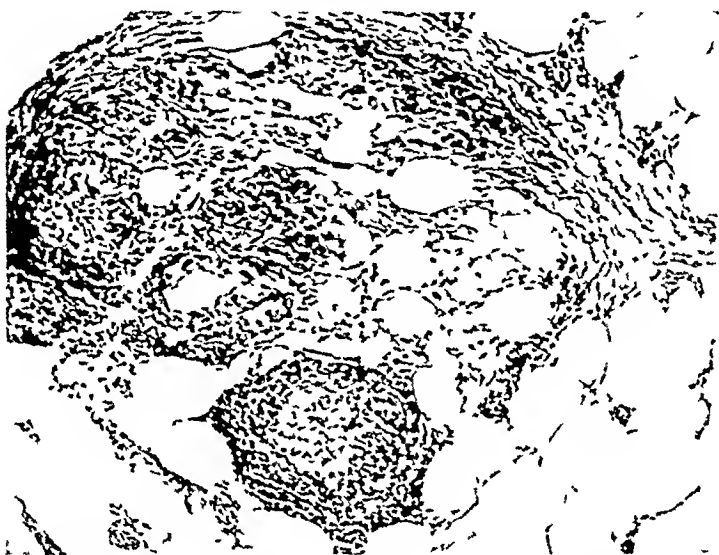


FIG. 2. Photomicrograph of a representative field in the subcutaneous fat at the site of a biopsied, indurated, and erythematous node. Within this field there are several contiguous nodules composed largely of fibroblastic and histiocytic cells and infiltrated by lymphocytes and occasional polymorphonuclear leukocytes, including some eosinophils. The adjacent fat tissue showed recent necrosis in places, beginning fibrosis, and infiltration by inflammatory cells.  $\times 100$ .

specimen. The lesions were distributed throughout the subcutaneous fat tissue principally in the form of clusters of milium nodules, some of which had a superficial resemblance to tubercles. Concerning the evolution of the lesion in question, it was stated that the latter apparently began as a subacute inflammatory focus infiltrated by small round cells and leukocytes, among which eosinophils were prominent. The fat cells in the involved areas were modified and were even replaced by foam cells. This was accompanied by the appearance of histiocytes and fibroblasts, resulting in the development of numerous discrete and conglomerate nodules. Multinuclear giant cells were prominent in relation to some of the nodules. Eventually, the lesion appeared to regress, leaving only fibrous scars and scattered small nests of foam cells as residua (figures 3A and B).

While no definitive diagnosis was ventured on the basis of this biopsy, it was felt that the subcutaneous nodules apparently represented some unusual and peculiar chronic inflammatory condition that was not in itself clearly tuberculous in character. It was suggested, furthermore, that the subsequent course might clarify the clinical picture as, indeed, proved to be the case.

With bed rest, recession of the skin lesions took place although they did not disappear altogether, and the patient was again referred to the Outpatients Department. With resumption of activity, however, she again developed new crops of lesions on the arms and legs. At about this time, the appearance of a group of tender, matted lymph nodes was noted.

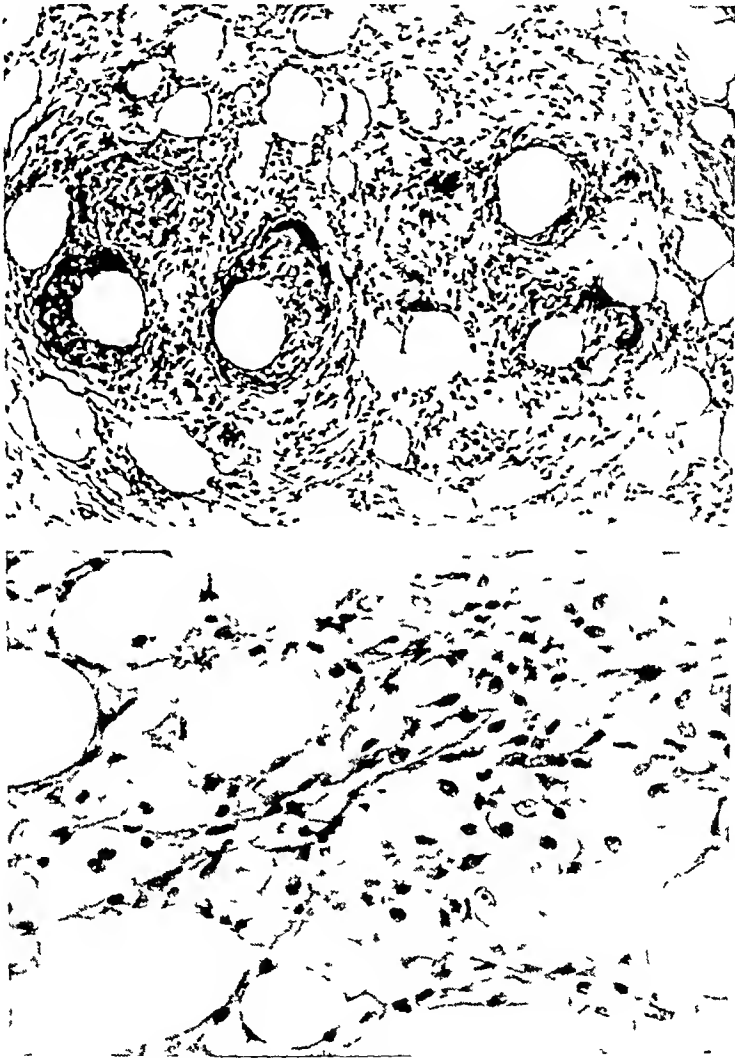


FIG 3A (Top) Photomicrograph of a representative field in a subsequent biopsy specimen showing a cluster of histiocytic nodules within the subcutaneous fat tissue. Multinuclear giant cells may be observed in relation to some of these nodules. Within the fat tissue generally, one observes evidences of inflammation and organizing fat necrosis, leading ultimately to fibrosis and the appearance of nests of foam cells.  $\times 100$ .

FIG 3B (Bottom) Photomicrograph of a field from the lesion illustrated in figure 3A, showing a nest of foam cells reflecting the organization of fat necrosis.  $\times 150$ .

in the left supraclavicular region where a biopsy had been taken previously (the one showing a picture suggestive of Hodgkin's disease). There were also a few palpable lymph nodes in the anterior triangle of the neck, in the left axilla, and in the left inguinal region.

*Fourth admission* (February 4, 1941 to February 22, 1941). At this time, several enlarged supraclavicular lymph nodes were excised for biopsy, as was also a wedge of skin and sub-

cutaneous fat tissue from the back of the calf where a discrete, hard subcutaneous nodule had been palpable.

Sections of all the lymph nodes submitted showed areas of caseous necrosis and numerous discrete and conglomerate tubercles, clearly indicative of tuberculous lymphadenitis. This impression was verified by guinea pig inoculation (figure 4B).

*Fourth skin biopsy.* The skin biopsy taken on this occasion revealed an area within the subcutaneous fat, presenting a cluster of tiny, pale yellow nodules, varying in size from pin point to 2 mm in diameter. Microscopic sections of these lesions showed changes within the fat resembling those described in the previous biopsy, and it was felt that the lesion should be classified under the head of erythema induratum (Bazin), a condition usually held to represent a peculiar cutaneous manifestation of tuberculous infection.

Whereas the nature of the skin lesions and the associated lymphadenopathy now seemed established, it was decided to treat the patient by desensitization to tuberculin. The first dose administered (on April 12, 1941) consisted of 0.1 cc. of Old Tuberculin in a dilution of one to a billion. The injections were given three times a week at two day intervals, the second dose being 0.12 cc. and the third 0.16 cc. Following the third dose, an afternoon rise in temperature to 100° F. occurred and the next dose was therefore reduced to 0.14 cc. The subsequent doses administered were 0.18, 0.24, 0.32, 0.42, 0.54, 0.68, 0.80 and 1.0 cc., respectively. The tuberculin dilution used was freshly prepared each week and, when 1.0 cc. of a given dilution had been reached, a dilution ten times stronger was prepared. No systemic reaction was observed until January 9, 1942 (almost nine months after therapy was instituted), when the patient had a chill and a temperature of 102° F., associated with diarrhea. These untoward manifestations may have been coincidental, however, since treatment was resumed, continuing with gradually increasing doses, without any further difficulty. On February 3, 1942, a dose of 1.0 cc. of undiluted Old Tuberculin was administered. This dose was repeated at weekly intervals on three occasions with no local, focal or systemic reactions. The treatment was discontinued at this point. In the course of desensitization, the skin lesions and the enlarged lymph nodes gradually disappeared. On February 1, 1943, the tuberculin test was found to be entirely negative with antigens of both human and bovine strains.

The patient was seen subsequently on many occasions and is still under observation. She enjoys good health, is at work, and travels a good deal. Her chest is clear. The pelvic mass which she presented originally is no longer palpable and causes no subjective complaints. At no time has there been any recurrence of the skin lesions or enlargement of lymph nodes. A tuberculin test done recently (December 24, 1947) was definitely positive (human and bovine antigens) in dilution of 1:1,000 and slightly positive in dilution of 1:10,000. Even though the patient is apparently no longer completely desensitized, however, she is still entirely well clinically and over six years have now elapsed since tuberculin desensitization was discontinued.<sup>2</sup>

#### DISCUSSION

The treatment of erythema induratum by desensitization to tuberculin was enthusiastically advocated as early as 1905 by Whitfield (4), McCull-Anderson (5) and others (6), who pointed out that the condition may respond unusually well to such treatment. Tuberculin therapy is at present largely neglected and many clinicians confronted with the problem of treating erythema induratum are likely to adopt a "laissez faire" attitude or resort to ineffective nonspecific symptomatic treatment, employing ultraviolet and X-ray irradiation, as well as various lotions and ointments. More recently (7) an attempt has been made to treat the condition by chemotherapeutic agents such as promizol and streptomycin, but the use of the latter has apparently not resulted in any lasting benefit.

<sup>2</sup> The patient was last seen by one of us (TTF) on December 28, 1948. She is clinically well. There were no recurrences of the skin lesions.

The current neglect of tuberculin therapy stems largely from unfamiliarity with its benefits, but apparently also from therapeutic failures, some of which, at least, are attributable to inaccurate diagnosis or to faulty judgment and, particularly, to undue haste in planning the course of treatment. As Montgomery, O'Leary and Barker (3) have emphasized, before embarking on a long program of tuberculin desensitization in a suspected case, one should require as evidence of the presence of erythema induratum, in addition to a positive tuberculin reaction (1) biopsy of one or more cutaneous erythematous nodes showing the histopathologic picture associated with the condition, and (2) proof, or at least presumptive evidence, of active tuberculosis elsewhere in the body.

As for the therapeutic management, it cannot be emphasized too strongly that tuberculin desensitization, if it is to be effective, must be prolonged and cautiously administered, preferably by a single observer, carefully avoiding even slight local or systemic reactions. So planned and administered, the method is not hazardous, as some have apparently felt. In the present case, the initial dose of Old Tuberculin, as noted, was no more than 0.1 cc. of a dilution of 1:1,000,000 (1:10 (9)) and the increments were so small that almost a year was required to achieve gradual desensitization. During that period, only one febrile episode was noted, during the ninth month of treatment. Indeed, even this episode may have had no relation to the tuberculin therapy, since the latter was resumed shortly thereafter without any untoward reaction. The rationale for tuberculin desensitization is the elimination of undesirable and disturbing allergic manifestations and the furtherance thereby of natural immunologic control of the tuberculous infection. On the other hand, we do not intend to convey the impression that tuberculin desensitization will invariably result in as gratifying a clinical response as was obtained in the case reported. Obviously, the result will also depend largely on the virulence of the infecting organism, a variable factor that can be determined only empirically (8). Furthermore, it appears that there are occasional patients who are so exquisitely sensitive to tuberculin that they seem incapable of being completely desensitized (9). There is a possibility that the favorable therapeutic response in our case was due in a measure to the fact that our patient *never was* very sensitive to tuberculin.

It may be questioned by some, since erythema induratum is a condition characterized by spontaneous remissions, whether tuberculin desensitization is to be credited with the gratifying clinical result in this case. That is a valid reservation, to be sure, but in support of our view it may be pointed out that the patient has remained completely free of all clinical manifestations of her disease for the past six years, whereas previously she had never been entirely free of complaints at any time, and during the two years preceding tuberculin therapy had been developing recurrent crops of erythematous nodes with great regularity.

The Hodgkin-like picture observed in the supraclavicular lymph nodes prior to the development of indubitable tuberculosis within the same group of nodes, is of unusual interest (figure 4A). The eight year interval that has now elapsed without the appearance of any manifestations of Hodgkin's disease and the continued good health of the patient would seem to exclude fully conclusively any possibility of Hodgkin's lymphoma. On the other hand, the relevant lymph nodes apparently did not contain tubercle bacilli at that time, inasmuch as guinea pig inoculation was negative. It is equally certain that the lymph nodes reappearing subsequently at the same site did show tuberculous infection since the pathologic evidence, already clearly indicative of caseating tuberculosis, was further substantiated by repeated guinea pig inoculation (figure 4B). In all probability, we are dealing with a peculiar and unusual hyperplastic forerunner of tuberculous lymphadenitis.

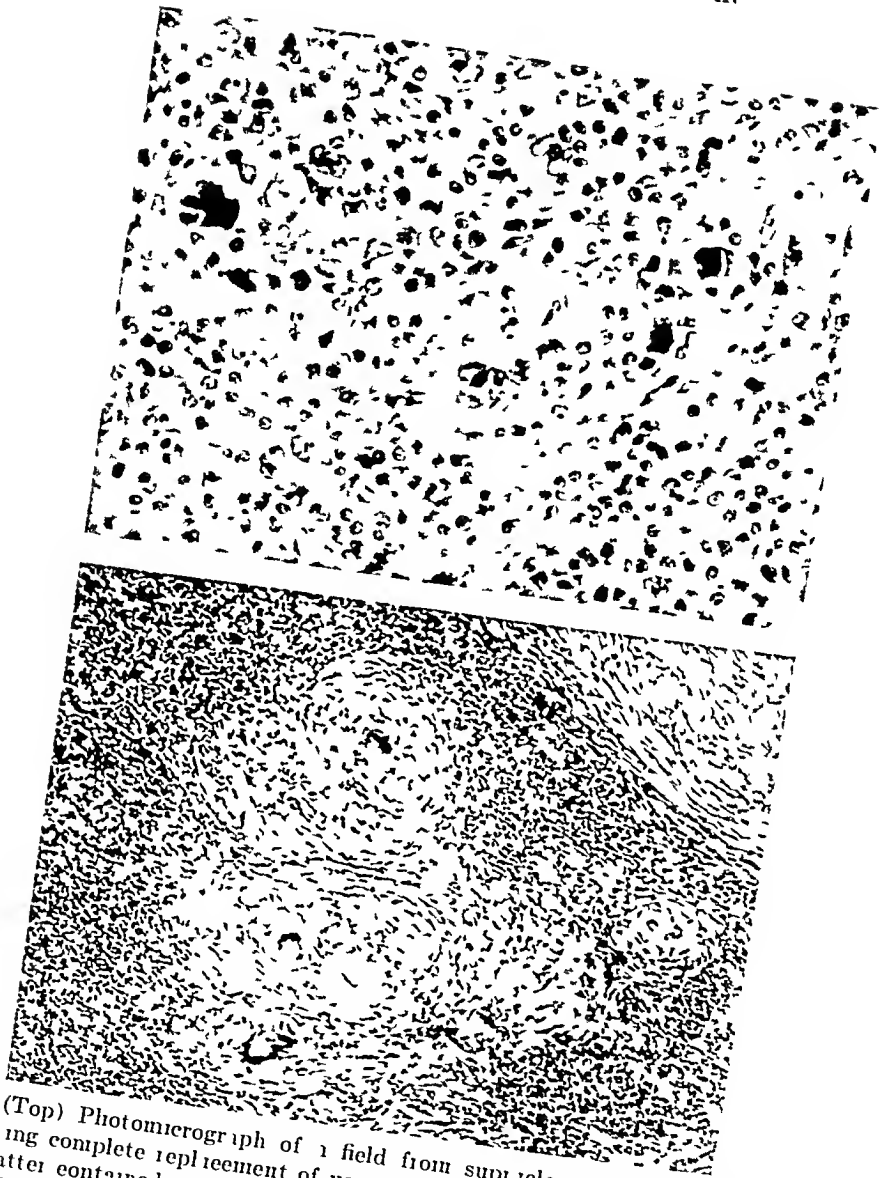


FIG 4A (Top) Photomicrograph of a field from suprapubic lymph node (first biopsy) showing complete replacement of normal architecture by a pleomorphic cellular tissue. The latter contained numerous mononuclear and multinucleated cells, apparently of reticulum cell origin, presenting large pale nuclei with reddish nucleoli. It was the appearance of these cells particularly that suggested the possibility of Hodgkin's disease.  $\times 500$

FIG 4B (Bottom) Photomicrograph of enlarged lymph nodes which recurred at the same site about a year later, showing clear cut, crusting, tuberculous lymphadenitis.  $\times 75$

#### SUMMARY

This paper deals with a pathologically proved case of erythema induratum (Bazm), associated with tuberculous lymphadenitis, in which an apparent "cure" was obtained by gradual desensitization with tuberculin. The patient has been followed clinically for over

eight years, during the last six years of which she has remained free of all clinical manifestations of the disease. The histopathologic picture of the cutaneous lesions in various stages of their evolution is described. The cutaneous lesions, at least as they manifested themselves in this case, seem to represent a peculiar, recurrent form of nodular panniculitis, developing apparently as a reaction to tuberculous toxins or allergens elaborated elsewhere in the body.

The development of tuberculous lymphadenitis was preceded by a peculiar hyperplastic reaction in the same group of lymph nodes, which simulated Hodgkin's disease.

#### SUMARIO

*Eritema Indurado (Bazin) Comunicación de un Caso Comprobado Asociado con Linfadenitis Tuberculosa y Completamente Ahogado con la Desensibilización con Tuberculina*

Este trabajo versa sobre un caso comprobado patológicamente de eritema indurado (Bazin), asociado con linfadenitis tuberculosa, en el cual se obtuvo una "curación" aparente mediante la desensibilización gradual con tuberculina. La enferma ha sido mantenida en observación clínica por más de ocho años, durante los últimos seis de los cuales ha permanecido sin la menor manifestación clínica de la dolencia. El cuadro histopatológico de las lesiones cutáneas en varias etapas de su evolución es descrito. Dichas lesiones, por lo menos tal como se manifestaron en este caso, parecen representar una forma recurrente, peculiar de paniculitis nodular que constituye aparentemente una reacción a las toxinas o los alérgenos tuberculosos elaborados en alguna otra parte del organismo.

La aparición de linfadenitis tuberculosa fué precedida de una peculiar reacción hiperplásica en el mismo grupo de ganglios linfáticos, que simuló enfermedad de Hodgkin.

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# PULMONARY ADENOMATOSIS<sup>1</sup>

## Report of a Case

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### INTRODUCTION

Pulmonary adenomatosis is a diffuse neoplastic disease of the lungs, affecting the bronchiolar and alveolar lining cells. It is regarded as a relatively uncommon disease in man. In 1947, Simon (1) reported a case of pulmonary adenomatosis in man, at which time he stated that ten cases had been previously reported, in all of which, except one, the diagnosis was established at autopsy. Hildebrand (2), in a later report of a case, estimated that a dozen cases of this disease had been reported. It is very likely that more cases of this disease exist than the literature would lead us to expect. Especially because of its resemblance to pulmonary tuberculosis and the fact that some of these cases must find their way to tuberculosis hospitals, a greater awareness of the disease on the part of sanatorium physicians should disclose a higher incidence.

Although the disease bears some pathological similarity to a disease of sheep, variously known as Jaagsiekte, epizootic adenomatosis, and infectious adenomatosis, a relationship between the two has not been established.

Jaagsiekte, as pointed out by Dungall (3), was found to be infectious and due to a pneumotropic virus, strictly limited to the lungs and bronchi of sheep, and transmitted through the expiratory air. No such transmissibility in man could be ascertained.

Pulmonary adenomatosis in man has the characteristics of a multicentric neoplastic process. Taft and Nickerson (4), in considering the relationship of this disease to carcinoma of the lungs in general, were of the opinion that no significance could be attached to this relationship. The majority of lung carcinomas, being bronchogenic in origin, arise from the bronchial or bronchiolar lining. Although some question exists as to the focus of origin of pulmonary adenomatosis, it is thought that it arises from the alveolar lining cells. Histologically, however, there is no sharp demarcation between the alveolar lining and the bronchiolar lining, so that origin from the goblet cells of the bronchiolar mucosa cannot be excluded and, with this in mind, a classification of terminal bronchiolar carcinoma would be tenable. This is especially important when it is considered that one of the basic symptoms is the expectoration of large quantities of thin, mucoid sputum, produced by the goblet cells.

As was indicated by Newberger and Geever (5), roentgenologic and bronchoscopic studies are of major importance in direct and differential diagnosis. If the roentgenographic and clinical picture suggests a diffuse pulmonary neoplasm and bronchoscopy discloses no involvement of the bronchial tree, the diffuse form of alveolar tumor should be considered, especially where the clinical picture presents a recurrent bronchopneumonic process (6).

The following case report brings into evidence certain clinical features, which may provide some enlightenment regarding symptomatology, clinical course, and pathological findings. As was stated above, the recurrent pneumonic crises and the history of expectoration of large quantities of thin, mucoid sputum, are particularly worth recording.

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<sup>1</sup> From Pawling Sanatorium, Rensselaer County, New York.



FIG 1 (Upper left) Roentgenogram of October 30, 1946, when patient attended the out-patient clinic and a tentative diagnosis of pulmonary tuberculosis was made

FIG 2 (Upper right) Film of February 13, 1947, showing an established pneumoperitoneum

FIG 3 (Lower left) Film of May 6, 1947, following a pneumonic episode

FIG 4 (Lower right) Film of September 16, 1947. Last roentgenogram before death, indicating the progressive character of the lesion

#### CASE REPORT

The patient, Mrs. E. W., was a 29-year-old white housewife. Her family history was not significant. Except for usual childhood diseases before the age of 9, she had always been in good health.

In the eighth month of pregnancy, in July 1946, the patient suddenly developed acute pain in the right chest, accompanied by fever and chills. After being treated by her physician

physician, a chest roentgenogram was taken and she was told she had pneumonia and pleural fluid. On July 31, 1946, she gave birth to her third child. The delivery was uneventful and she went home in the usual time.

She felt well until October 1946, when she again had pain in the right chest, accompanied by cough and loss of weight. At this time also she noted a sudden expectoration of a large quantity of thin, watery sputum. Because of these complaints, she was referred to the outpatient clinic of Pawling Sanatorium. As the findings were suggestive of pulmonary tuberculosis (figure 1), admission for observation was arranged on November 7, 1946, approximately four months after the onset of her symptoms.

Physical examination on admission showed a 29 year old woman who was 5 feet 4 inches in height and weighed 114 pounds. Her usual weight had been 125 lbs. She appeared to be a normally nourished and developed white woman, except for extreme pallor, and the abnormal physical findings were confined to the lungs. There was bronchial type breathing over the right upper lobe, with increased whispered and spoken voice. Over the lower half of the right lung, there was flatness on percussion and breath sounds were absent. Posteriorly and anteriorly over the mid portion of the right lung, there were numerous fine rales, with egophony at the level of the fifth dorsal vertebra posteriorly. The breath sounds on the left were exaggerated, with a bronchial quality in the upper lobe, but no rales were heard. The heart was not displaced, was regular, and no murmurs were heard. The blood pressure in mm. of mercury was 104 systolic and 78 diastolic. Laryngeal examination was entirely negative.

A serologic test for syphilis (Wassermann) was negative. The erythrocyte count was 5,020,000 and the total leukocytes 12,300 per cu. mm. with a normal differential. The concentration of hemoglobin was 84 per cent (Sahli). The urinalysis was normal. Several sputum examinations were performed which were negative, but on December 16, 1946, a 72 hour concentration test was reported positive for acid-fast bacilli. Subsequently, monthly sputum examinations from January to July, 1947, were all reported as negative, except on February 12, 1947, when a few acid-fast bacilli were again reported, although cultures of the specimen were negative for tubercle bacilli.

The patient was kept on the usual sanatorium regimen but, because serial roentgenograms failed to show improvement and because of the bilateral dissemination of the disease process, pneumoperitoneum was instituted on January 16, 1947. A satisfactorily uniform pneumoperitoneum (figure 2) was maintained by weekly refills of air, during which time she demonstrated clinical improvement with gain in weight and normal temperature, although the physical findings were in no way affected.

On March 17, 1947, there developed an acute pneumonic exacerbation in the right lung, which responded to penicillin. There was a recurrence of this early in May, and a chest film of May 6, 1947, showed a progressive involvement of each lung (figure 3).

She was considered to have an unusual type of pulmonary tuberculosis, for which streptomycin was advised. Before deciding to undergo this treatment, she took a leave of absence from the sanatorium, without approval. She returned on July 11, 1947, exhibiting a deterioration of her physical condition, with increasing dyspnea, loss of weight, and increase of pulmonary findings, both clinically and by roentgenogram. The pneumoperitoneum was not maintained during her absence from the sanatorium and the air was allowed to absorb.

On July 14, 1947, she was started on 1.0 Gm. of streptomycin daily. Treatment, totaling 128 Gm., was continued without inhibiting the progress of the disease (figure 4). The only toxic manifestation was a slight dizziness. Increasing dyspnea and cyanosis required continuous administration of oxygen from August 20, 1947, until death on October 30, 1947.

#### *Necropsy Findings of Pleural Cavities and Lungs*

**Pleural cavities.** The right pleural cavity contained 50 cc. of cloudy pink fluid. The surfaces of the anterior part were smooth and glistening. The lateral and posterior right pleural space was obliterated by heavy fibroid adhesive webs which bound the lung to the chest wall. The right lung filled approximately one third of the pleural space.

The left interlobular pleural surfaces were smooth, pink, and glistening. There were several heavy fibroid bands, but most of the lung was free from adhesions. The left pleural space contained 250 cc. of cloudy pink fluid. The left lung filled approximately one-half the pleural space.



FIG 5 (Top) Lungs showing contraction with distortion. There is marked chronic pleuritis of the lower lobe of the right lung.

FIG 6 (Bottom) Cut surfaces of right and left lungs.

*Lungs* (figure 5) The right lung weighed 560 Gm. and the left 850 Gm. Both lungs were very irregular in contour and were markedly distorted. The surfaces were composed of nodular masses of reddish tissue which, on cutting, exhibited a finely granular, glistening surface. The middle lobe of the right lung was almost entirely replaced by this tissue and the lateral aspect of the lower lobe (right) was composed of granular, grayish-pink tissue which tore easily.

The cut surfaces (figure 6) were finely granular, firm and grayish-pink. The upper and lower lobes of the right lung and the upper and lower portions of the left lung were composed of firm, pink, glistening, moist lung tissue. Crepitation was present in these areas but was diminished.

The chief bronchial branches of each lung were encased in the grayish-pink tissue and their lumina were almost completely constricted.

The large pulmonary vessels were patent.

### *Microscopic Description*

*Lungs* In one section the pleura was thickened by heavy fibrous tissue heavily infiltrated by collections of lymphocytes. Each and every section of lung tissue showed the presence of large and small collections of atypical but quite well differentiated columnar epithelial cells (figures 7A and B). In places the cells appeared to be lining lung remnant. The cells showed a tendency to form polyoid or papillary projections which protruded into the lumina of the alveoli. In some places the normal lung architecture was lost and the alveolar walls were



FIG 7A (Left) Low power field showing the presence of large and small collections of atypical but quite well differentiated columnar epithelial cells, which appear to be lining lung remnant. The cells show a tendency to form polyoid or papillary projections, which protrude into the lumen of the alveoli.

FIG 7B (Right) High power field showing more detail.

replaced by large masses of atypical cells which showed a tendency to form papillary projections. In some situations, apparently the sites of oldest growth, there was fibroblastic activity and the tumor cells were supported by fibrous tissue. Sections from the hilum of the lungs showed large amounts of neoplastic tissue. In no instance could the origin of the tumor cells be traced to bronchial mucosa. Mitoses were occasionally seen. Blood vessel invasion was not noted.

In general the pulmonary alveoli were dilated and contained large numbers of mononuclear phagocytes, but no polymorphonuclear leukocytes were seen.

### DISCUSSION

From a clinical viewpoint, the lack of specific diagnostic criteria renders an accurate diagnosis of pulmonary adenomatosis very difficult. The roentgenographic findings *per se* present several problems in differential diagnosis. As contrasted with a solitary pulmonary tumor, multiple tumors, associated with the concurrent inflammatory changes, produce roentgenographic findings more characteristic of pulmonary tuberculosis than of neoplastic disease. The absence of tubercle bacilli, however, in view of the usual widespread roentgenographic findings, should lead one to suspect neoplastic disease. In addition, several of the cases reported presented the complaint of expectoration of large

quantities of thin mucoid sputum. Distant lymph node involvement by metastasis is almost always absent in pulmonary adenomatosis, so that biopsy for diagnostic purposes is precluded.

From the pathological viewpoint, the important consideration is the origin of the neoplasm, together with its proper classification. If this neoplasm arises from the bronchiolar mucosa, then the classification of terminal bronchiolar carcinoma is justifiable. Until the definite focus of origin is thoroughly established, pulmonary adenomatosis might be regarded as a distinct clinical and pathological entity.

#### CONCLUSIONS

1. A case of pulmonary adenomatosis in man is reported.
2. Diagnostic criteria are considered.
3. Pathological classification of this neoplasm is not yet completely established.

#### *Acknowledgement*

Gratitude is hereby expressed to Dr. Gustavus H. Kline, Jr., formerly pathologist at Samaritan Hospital, Troy, New York, for the necropsy report and his assistance in preparing the illustrations.

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## EDITORIAL

### Integration of Streptomycin with other Forms of Therapy for Pulmonary Tuberculosis

When streptomycin became available for extensive clinical investigation in pulmonary tuberculosis, the principal problem was to determine its therapeutic value in various forms of the disease. At the same time important collateral information was sought regarding toxicity and the emergence of streptomycin-resistant strains of the tubercle bacillus in treated patients. To these ends the original investigators limited their therapeutic efforts to the use of streptomycin and bed rest alone in the treatment of their earlier patients. It quickly became apparent to experienced phthisiologists that streptomycin exerts a favorable influence in pulmonary tuberculous lesions having a fresh exudative component. Many investigators, working cooperatively, have also demonstrated a marked therapeutic effect in ulcerative mucosal lesions of the respiratory tract, in disseminated nodular pulmonary lesions (whether acute, subacute, or chronic), and in miliary tuberculosis. Although toxic drug reactions were frequent in the original patients studied, these became a lesser problem after reduction in the daily dosage.

It soon became apparent, however, that even in the carefully selected early patients, relapse of disease was frequent and that streptomycin alone in addition to bed rest was not a definitive cure for tuberculosis in the majority of patients. As surmised by Hinshaw and others, streptomycin exerts only a temporary, albeit powerful, suppressive effect against the tuberculous process. The action of the drug is limited to the period of time during which the tubercle bacillus remains sensitive to it. If this time is sufficient, the patient's inherent resistance mechanisms may become dominant and effect a natural remission of disease following streptomycin treatment. If predominance of drug-resistant bacilli occurs early, the patient usually reverts to his pretreatment status. If he is still unable to cope with his disease by his own defenses, the result is further progression of the disease unchecked by additional streptomycin.

Because of technical problems, direct application of laboratory data on streptomycin resistance of the tubercle bacillus to the clinical problems confronting the physician must be made cautiously. Nevertheless, considerable evidence has been accumulated by various investigators which permits one to assume that *in vitro* resistance is tantamount to *in vivo* resistance in the great majority of patients whose organisms have developed resistance to 100 to 1,000  $\gamma$  of streptomycin per cc of medium. This conclusion is based principally upon (1) clinical and roentgenological relapse of patients during treatment simultaneously with the emergence of resistant tubercle bacilli in the sputum, (2) the failure of response after re-treatment with streptomycin among patients whose bacilli are known to be resistant as a result of a previous course of streptomycin. Once streptomycin-resistant strains of tubercle bacilli appear, they persist for months or years and may remain predominant indefinitely in a particular infection.

In various groups of patients, the incidence of emergence to predominance of highly resistant strains of tubercle bacilli may vary from 30 to 75 per cent in a given group. Upon analysis of the case material, this seeming discrepancy may be partially explained. In the early experience at the Laurel Heights Sanatorium, we were impressed with the high incidence of resistant organisms emerging in patients with gross caseation and cavity formation as contrasted with a group of patients with certain types of active, but relatively indolent, pulmonary disease without frank caseation or cavity formation. Similar relationships have been noted by others such as Woodruff, Riggins, Mitchell, and their associates. Obviously other factors do influence the emergence of resistant tubercle bacilli but at the present time it seems safe to assume, for practical purposes, that at least 60 per cent of the patients having gross caseation or cavitation will develop highly resistant strains of tubercle bacilli if treated by streptomycin and bed rest alone for a sufficient period of time. This seems true regardless of alterations in the dose regimen employed. Certainly the general experience has been that a reduction of the duration of treatment to 42 days from 120 days has not completely solved the problem of resistance. Resistant strains may begin to emerge as early as the thirtieth treatment day but are most likely to occur after six to eight weeks of treatment. Thus, in patients likely to develop resistant organisms, we can be certain of only about six to eight weeks of benefit from the suppressive action of streptomycin.

The use of combined therapy, such as para-aminosalicylic acid and streptomycin, or the advent of new drugs may eventually solve the question of streptomycin resistance. At the present time, however, the phenomenon remains a major problem.

Secondary only to the problem of resistant organisms in streptomycin treatment of pulmonary tuberculosis is the high incidence of relapse of the patient's disease after treatment with streptomycin has been completed. Among a group of 88 of our patients observed twelve to twenty-seven months after completion of streptomycin therapy, a definite roentgenological and bacteriological relapse occurred in 62 per cent of those with frankly caseous or cavitory disease when treated by streptomycin and bed rest alone. If gross caseation and cavitation (as judged by chest roentgenograms) were not present before treatment, however, a quiescent or arrested status was achieved by 67 per cent of the patients. Over-all relapse rates among patients treated by streptomycin and bed rest alone have been reported by others to range from 30 to 60 per cent. It is obvious from these data that the patient with frankly caseous or cavernous disease, who has demonstrated poor response to bed rest alone, is unlikely to achieve sustained arrest of his tuberculosis by the mere addition of streptomycin to the rest regimen.

The majority of sanatorium patients in whom the use of streptomycin is most urgently needed have pulmonary disease of a mixed type of pathology. Usually the basic lesion is of a fibro-caseous-cavernous type with an additional component of a more exudative reversible type of disease. Occasionally the therapeutic problem is one of blocked or tension cavities, presumably the result of endo-



bronchial involvement in association with parenchymal disease. Perhaps our greatest therapeutic problem is the patient with active cavitory disease which is suitable for collapse, but should not be collapsed because of the presence of recently progressive contralateral disease. These various types of involvement comprise, in a large measure, the chief problems of the physician treating pulmonary tuberculosis. How may streptomycin be used most wisely in this large group of patients needing some additional aid to effect a natural remission of their disease?

It is in patients with the above categories of disease that the temporary suppressive action of streptomycin is most limited in duration by the frequent emergence to predominance of streptomycin-resistant strains before the patient's inherent resistance mechanisms become dominant. It is also in this type of disease that post-treatment relapse is most common. Thus it is incumbent upon the physician to evaluate carefully the potentialities of streptomycin and bed rest alone in a given case. Is he willing to sacrifice streptomycin sensitivity for a short duration of clinical and roentgenological improvement in a patient who is ill with a disease known to be of a chronic relapsing nature? Had he not better plan his therapeutic program on the basis of a six to eight week period of suppression of disease by streptomycin and, during this period, attempt to accomplish some more definitive form of treatment? All too many patients are entering sanatoriums who have had a prior course of streptomycin, experienced temporary clinical or roentgenological improvement, developed streptomycin-resistant infections, relapsed, and thus have lost the golden opportunity for collapse therapy once afforded them by streptomycin.

In a majority of patients with disease of a purely disseminated character without cavitation, the addition of streptomycin alone to the usual bed rest regimen will often be sufficient to reverse an unfavorable trend and permit the patient to achieve true arrest of his disease. Response is usually equally satisfactory and relapse rate is low in patients treated promptly for fresh exudative noncavitory lesions. Moreover, the emergence to predominance of drug-resistant strains of tubercle bacilli are less likely to be encountered following treatment of such patients.

The great majority of patients in whom the use of streptomycin is contemplated should have a careful over-all appraisal of their disease. This requires prior consultation between the physician and the thoracic surgeon. A complete plan of treatment should be outlined predicated upon (1) the known suppressive action of streptomycin against the more responsive types of pulmonary tuberculosis, and (2) the known effective collapse measures in cavitory or caseous disease.

If the patient's disease is of a sufficiently destructive nature to warrant thoracoplasty or resection, yet his poor clinical condition or active contralateral disease precludes such an immediate procedure, streptomycin may prove an invaluable agent in bringing him to major surgery. Once the objective, thoracoplasty or resection, has been decided upon all concerned should adhere strictly to the therapeutic plan. With initial symptomatic, bacteriologic, and

roentgenologic improvement frequent in the majority of well selected patients receiving streptomycin, the physician, as well as the patient, may feel that major surgery may be avoided. This hope may be fulfilled in a minority of patients but at present we cannot predict which patient will fall into this fortunate group. All too frequently the patient relapses during treatment, has developed streptomycin-resistant tuberculosis, and is unresponsive to further therapy with this agent. Likewise, the conservative surgeon must be convinced that once a favorable trend has become manifest, usually after three to four weeks of streptomycin treatment, he may perform the thoracoplasty or resection with a fair degree of safety, even though there has recently been active or progressive disease in the same or opposite lung. Experience in this and other clinics (Levine, Klein, Froman) has demonstrated that such a procedure is practicable and reasonably safe. One need not wait for a definite favorable roentgenological change in the relatively good lung. If an initial favorable clinical response is noted and the minor lesion in the better lung is of the type of noncavitary disease known to be responsive to streptomycin, one should proceed immediately with surgery while still enjoying the benefits of streptomycin.

If the initial response to streptomycin proves disappointing and major surgery still seems contraindicated after about six weeks of treatment, it may be well to attempt a minor collapse procedure such as phrenic-pneumoperitoneum. This may eventually result in sufficient stabilization of the patient's disease to permit major surgery at a later date. In such a patient it would seem prudent to discontinue streptomycin on the assumption that a high proportion of the remaining bacilli are drug-resistant. Even if this has not occurred, however, it is advisable to discontinue chemotherapy in order to save the remaining period of suppressive action of the drug for use at some later date.

In other patients, over-all assessment of the problem may result in a decision to use pneumothorax or phrenic-pneumoperitoneum as a definitive treatment. If this be the case, one should integrate the selected procedure promptly in order to receive maximum benefit from the combination of streptomycin and collapse. Obviously, not all patients require streptomycin in conjunction with these procedures but in the acutely and severely ill patient the usual "cooling off" period before collapse measures are instituted may be shortened by its use. In our limited experience, however, pleural complications have not been avoided by a preliminary course of streptomycin before collapsing the acute lesion.

Favorable response of visible endobronchial tuberculosis suggests the use of streptomycin in conjunction with pneumothorax for the treatment of tension cavities. Results to date in a limited number of patients have been disappointing but the problem is worthy of further investigation.

In a large series of patients who were "standard risk" thoracoplasty candidates, the routine use of streptomycin as a prophylactic measure in the Veterans Administration produced but a very slight lowering of complications in the treated patients when compared with alternate controls. It would seem more intelligent to reserve streptomycin for the treatment of complications when they occur.

In the standard resection candidate, especially with tuberculous endobron-

chial disease, the use of streptomycin prior to, and for a few weeks following, the operation may be beneficial in lessening immediate postoperative complications. There is no evidence as yet that such treatment will affect the major problem of long term relapses.

The present tendency to give a course of streptomycin and see what it will do is to be deplored. Each patient should be carefully appraised and an over-all plan of treatment be outlined based upon close integration of the temporary suppressive action of streptomycin with known effective collapse procedures. Once decided upon, the plan should be followed to its predetermined objective despite a temporary improvement with streptomycin alone. In this manner we will have (1) fewer patients obtaining only temporary improvement at the price of developing drug-resistant tuberculosis, (2) more patients obtaining maximum benefit from streptomycin therapy, simultaneous control of their disease by collapse treatment, and a better chance for permanent arrest of their disease.

Until a new agent effective against streptomycin-resistant strains of the tubercle bacillus becomes available, or until we can delay the emergence of resistant strains by the simultaneous administrations of two or more drugs, we should use the temporary opportunity frequently presented by streptomycin to accomplish during that period all we can toward a definitive cure of the patient. Thus it seems wise to heed the advice of Horace, "Seize now and here the hour that is, nor trust some later day."<sup>1</sup>

JOHN B. O'CONNOR

<sup>1</sup>"Carpe diem, quam minimum credula postero" Ode XI, Leuconoe

## LETTERS TO THE EDITORS

### A PYRIDINE DERIVATIVE AND EXPERIMENTAL TUBERCULOSIS

*To the Editors of the American Review of Tuberculosis*

Antibiotic action in tuberculosis reached a new height with the advent of streptomycin and dihydrostreptomycin, yet there are many phases of the action of these substances *in vivo* which are not clearly defined nor understood today in the simple sense of a direct chemotherapy. Their peculiar localized effects *in vivo* on tuberculosis, their inability to destroy tubercle bacilli in relatively high concentrations *in vitro* as well as *in vivo*, the fact that the tubercle bacilli can develop a resistance toward high concentrations *in vitro* and *in vivo* in a relatively short time, and that the persistence of the effects *in vivo* are not dependent upon adequate concentrations of the antibiotic are intriguing. Such information warrants further studies to disclose the mechanism of chemotherapy in the hope of overcoming some of the inadequacies in treating tuberculosis with these agents.

Recently a highly potent *in vitro* static pyridine was described in the form of 2-butoxy-5-amino pyridine sodium formaldehyde bisulfite (ABF) which apparently lacked action *in vivo*, as deduced from inconclusive feeding experiments (Harry W. Feinstone, *Proc Soc Exper Biol & Med*, 1946, 63, 153; Duca et al., *Proc Soc Exper Biol & Med*, 1948, 67, 159). The treatment was begun a week after heavy subcutaneous infection and consisted of two incompletely spaced injections on the basis of blood analyses, and in amounts producing local ulcers. The lack of adequate explanatory experiments made it appear advisable to pursue further studies with it. Accordingly, it was found that the medium played an important part in the results with  $\alpha$ -diaminopyridine monohydrochloride (PDM). The action of this pyridine resembles streptomycin and dihydrostreptomycin which, even under standard planting of acid-fast saprophyte (Day) and human tubercle bacilli as test organism, varies in different mediums. However, this variable effect on nutrients was not so great in the case of ABF. The greater stability of ABF in *in vitro* action in a range of different mediums was further noted in the nearly equivalent effects upon the acid-fast saprophyte (Day) and the human tubercle bacilli. In relatively high concentrations, 10 mg per cc, which is about 1,000 times the retarding concentration, contained in a nonprotein simple nutrient medium (Wong-Wemzirl), ABF destroys the viability of the acid-fast saprophyte Day in about three to six days at 37° C. Concentrations below 10 mg per cc (0.1 mg per cc in over four days) require much longer exposure to destroy the viability of these acid-fast bacilli. ABF is a more efficient tuberculocide than streptomycin. On human tubercle bacilli, ABF acts about the same as on the acid-fast saprophyte, although its potency appears to be slightly greater in that viability is destroyed by 1.0 mg per cc concentration within six to ten days and 0.1 mg per cc succeeds within twenty to forty days. It appears also to be a more potent retardant of the growth of human tubercle bacilli *in vitro* in simple nutrient mediums than streptomycin. In order to test the neutralizing effect of tissues upon ABF, various amounts were mixed with one gram of ground guinea pig tissues, and growth inhibition was tested against the acid-fast saprophyte Day planted in concentrations of 0.02 mg of suspension per cc. The findings indicated that ground liver and kidney tissues could neutralize the retarding action of more than 0.01 mg of ABF, whereas the retarding action remains at about 0.001 mg for lung, spleen, brain, and blood. This neutralizing effect was also noted for ground liver tissue against streptomycin when one gram of tissue abolished the effect of 50 units (50

$\gamma$ ) of streptomycin (Corper, H J, and Cohn, M L, Yale J Biol & Med, 1946, 19, 1, Corper, H J, and Cohn, M L, J A M A, 1948, 137, 357)

Following the intravenous (or subcutaneous) injection of relatively large amounts (135 mg) of ABF, the retardant effect persisted for only a comparatively short period of time (never exceeding six hours) After oral administration, it was not discernible

In view of the fact that ABF showed a definite and constant *in vitro* retarding effect upon the growth of the acid-fast saprophyte Day and the human tubercle bacilli in simple nutrient mediums, and that its retarding effect was discernible also in the blood and certain tissues following its injection subcutaneously, it appeared advisable to follow these effects by treatment experiments in guinea pigs For this purpose we used the decisive intravenous (ear vein) infection method of giving virulent tubercle bacilli in fine suspension to guinea pigs (Corper, H J, and Cohn, M L, J A M A, 1945, 127, 1043)

The results of this treatment study with ABF in intravenously infected guinea pigs indicate that ABF given in a single daily amount of 20 mg subcutaneously was without appreciable effect upon either the tuberculous lesions or the fatal issue produced by the intravenous injection of one milligram of virulent human tubercle bacilli In order to further correlate treatment with the persistence of the ABF action in the blood, the repeated administration of 20 mg at two-hour intervals subcutaneously was tried (total daily dose, 240 mg) These intensive treatments with ABF also proved to be without effect on the tuberculosis and appeared to hasten the lethal issue in the animals slightly It is to be noted also from these studies that the ABF was without appreciable effect on spleen size in the treated animals except for the intensive treatment series where a perceptible but not marked splenomegaly resulted This study likewise revealed that the ABF treatment was without beneficial or detrimental effect upon the results obtained with streptomycin used coincidentally in 25,000 unit amounts daily However, in spite of the long combined treatment period and evident absence of marked gross tuberculosis in these animals, cultures of tubercle bacilli were obtained from all the important organs in these animals and the strains of tubercle bacilli isolated from these animals proved streptomycin-resistant

A similar treatment experiment was performed with guinea pigs using phenyl azo  $\alpha$  diaminopyridine monohydrochloride, PDM, as therapeutic agent given both by subcutaneous injection and orally in pure powder form in No 5 gelatine capsules to a total of 100 mg per day The presence of PDM in the blood and urine could be recognized easily by its color, and its presence was determined by the retarding effect on the growth of the acid-fast saprophyte "Day"

PDM is, without appreciable effect, upon the tuberculosis resulting from the intravenous injection of 10 mg of fine suspension of virulent human tubercle bacilli (\*4008) even when given in amounts imparting a decided yellow color to the tissues in general The PDM was also without effect on the lethal issue resulting from the intravenous injection of the human tubercle bacilli When given in large amounts orally, this effect was hastened

It appears from the foregoing studies with PDM that, even though a chemical agent is a good retardant to the growth of acid-fast saprophytes and tubercle bacilli in a relatively poor nutrient medium and its presence is indicated in sufficient amount for similar retardation of the growth of tubercle bacilli, such retardation of the tubercle bacilli *in vivo* or of the disease tuberculosis does not occur This is probably because the complex colloidal nature of the body fluids and tissues precludes such action, which would appear to be suggested by the facts that the guinea pig is naturally highly susceptible to infection with virulent mammalian tubercle bacilli and that the retardant effect noted for relatively

poor nutrient mediums is almost completely negated when the PDM is incorporated in a good nutrient medium such as the egg yolk. And this is in spite of the evident fact that the PDM appears to be present sufficiently in the free state to retard in amounts acting in a poor nutrient

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# THE AMERICAN REVIEW OF TUBERCULOSIS

## ABSTRACTS

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### CLINICAL STUDIES, TUBERCULOSIS

**Tuberculous Pleural Effusion**—Tuberculous pleural effusion is rare in childhood. One-half of the cases are seen between the ages of 15 and 25. About 25 per cent develop pulmonary tuberculosis within five years, up to 10 per cent succumb. A total of 149 cases were seen by the author. They were divided according to age as follows: early school (5 to 8 years), 18 cases; late school (9 to 13 years), 37 cases; early adolescence (14 to 15 years), 36 cases; and adults (16 years and over), 58 cases. There was a predominance of males in all groups, greatest in the younger and decreasing with advancing age. Likewise, the incidence of a history of family contacts decreased with advancing age. Only one patient had erythema nodosum. The tuberculin test was positive in 84 of the 91 children, in the other 7 it was not done, as tuberculosis was proved by other means. The sputum showed tubercle bacilli in 2 children and 3 adults. There was a lower percentage of gross effusions in children than in adults but 91 per cent of the youngest group showed hilar nodes as compared to 38 per cent of the older patients. In the youngest group, no pulmonary infiltrations were seen, the incidence rose to 24 per cent in the adult group. No calcifications were seen in the children's roentgenograms. Other tuberculous involvements, such as bone and joints and cervical and abdominal lymph nodes, were very infrequent and were equally divided between children and adults. All the patients were given general sanatorium care. During a follow up of four years or more none of the children in the two younger groups, 55

per cent of the early adolescents, and 11 per cent of the adults developed pulmonary tuberculosis.—*A study of tuberculous pleural effusion in children and adults, N Landau, Tubercle, February, 1949, 30: 26*—(A G Cohen)

**Primary Complex and Bronchoscopy**—Bronchoscopy has greatly elucidated the pulmonary manifestations which follow the primary tuberculous infection. In uncomplicated primary infections, the orifice of the bronchus to the lobe where the primary focus is located usually is slightly congested and edematous, showing a mucous secretion rich in polymorphs and macrophagocytes. In cases of chronic epituberculosis, edema of the main bronchus of the diseased lobe is predominant and the narrow central opening may be obstructed by a plug of tightly packed macrophagocytes. The bronchial glands perforate and form fistulas much more frequently than was presumed. These small fistulas may be single or multiple and form simultaneously or successively. Their presence is suggested by paroxysmal cough, a "stitch in the side," temperature, and transient expectoration of sputum containing tubercle bacilli. Many of these minute fistulas soon stop discharging and close within a few months. Some openings obliterate, others remain visible as scars. Glandular dissemination may leave multiple calcifications in the lung field concerned. Bronchiectases may form subsequent to chronic epituberculosis, atelectases, calcified hilar glands and fibrosis.—*Effect of bronchoscopy on the primary complex and its sequelae, A G Cohen, Tubercle, February, 1949, 30: 26*



*cours des périodes primaire et secondaire de l'infection tuberculeuse*, A Dufourt & P Moumer-Kuhn, *Schweiz Ztschr Tuberk*, 1948, no 2 65 —(E Dunner)

**Endobronchial Tuberculosis**—As judged by bronchoscopic and roentgenographic observations, endobronchial tuberculous lesions began in the surrounding lung tissue in the majority of 20 patients. Emphasis is placed on the fine or coarse infiltrations seen in the pulmonary tissue in the immediate vicinity of the hilum. If a progressive pulmonary lesion exists simultaneously with the tuberculosis of a draining bronchus, the use of pneumothorax appears justified but it is to be avoided if an endobronchial lesion exists independently —*Ein Beitrag zur Kenntnis und Therapie der Bronchustuberkulose*, H Rechenberg & A Labhart, *Schweiz Ztschr Tuberk*, 1949, no 1 29 —(E Dunner)

**Constrictive Pericarditis**—There are 3 forms of chronic pericardial disease asymptomatic, constrictive (*concretio cordis*), and *accretio cordis*. In the asymptomatic type, the pericardial cavity is obliterated by fine adhesions. The parietal and visceral layers are not thickened or closely adherent. This type is seen in old myocardial infarction and in some unidentified diseases. In constrictive pericarditis the heart is normal or reduced in size. It is encased in a greatly thickened dense fibrous pericardium which is not adherent to the chest wall. The etiology is almost always tuberculosis. In *accretio cordis* the heart is enlarged, it is encased by a moderately thickened pericardium, the two layers of which are adherent and are attached to the chest wall. The etiology is almost always rheumatic fever. This article is concerned with constrictive pericarditis. In previously reported cases, there was no evidence of rheumatic fever, uremia, infarction or malignancy. Histological examination gave no clue as to the etiology. No patient gave a past history of pericarditis. To determine the etiology, the authors decided to trace the course of the disease which was the probable origin, namely acute tuberculous

pericarditis. In its simple form, this is a fairly benign disease, often difficult to differentiate from constrictive pericarditis. The pericarditis frequently is part of the syndrome of polyserositis which is a more serious condition. In either type, it is difficult to find tubercle bacilli. The circulatory effects are like those of constrictive pericarditis, the venous pressure never falls to normal nor does the liver return to normal size. Of 18 cases of acute tuberculous pericarditis, including 4 without and 14 with tuberculosis of other serous cavities, 16 developed constrictive pericarditis. The heart shadows became smaller with less intense pulsations. Engorgement of neck veins and ascites were characteristic. Seven patients with polyserositis were not operated upon and all died of widespread tuberculosis in seven months to five and one-half years. In 9 cases, operation was performed. In all but one, active tuberculosis of the pericardium was encountered. Preoperatively, it could not be determined whether or not the tuberculous process had healed. There were 3 operative deaths. Of the other 6 patients, 2 developed tuberculosis elsewhere in the body. The risks of tuberculous spread are thought to be exaggerated. The policy is to delay operation as long as possible but not unduly long. Of 7 patients with acute septic pericarditis in the terminal stage of sepsis, 5 died and 2 recovered. Neither of the surviving patients developed constrictive pericarditis. The authors doubt the existence of acute idiopathic pericarditis —*The aetiology of constrictive pericarditis, with specific reference to tuberculous pericarditis, together with a note on polyserositis*, G W S Andrews, G W Pickering & T H Sellors, *Quart J Med*, October, 1949, 17 291 —(A G Cohen)

**Tuberculosis of Greater Trochanter**—Tuberculosis of the greater trochanter of the femur with involvement of the overlying bursa was found in about 0.2 per cent of cases of tuberculosis. The authors report 12 patients averaging 28 years of age, the youngest being 7 years old. It is thought that trauma was a causative factor in several

of the patients although many had tuberculosis in other locations. Usually the patients noticed a swelling over the trochanter or complained of pain over the outer aspect of the thigh. A fluctuant swelling usually was found extending backward over the buttock, a sinus was sometimes present. Movements of the thigh were unaffected but passive adduction often produced considerable pain. Roentgenograms showed erosion of the periphery of the greater trochanter or an encysted area in the middle of the trochanter. Drainage was instituted in 3 cases before the nature of the lesion was ascertained. None of the lesions healed and all were excised later. Aspiration in 3 cases was followed by sinus formation and excision was performed. Incision and curettage of the walls of the abscess were done in 5 cases with healing in 4, in 2 by primary intention. In 7 cases the bursa and the involved portion of the trochanter were excised. This was done also in one case of tuberculous osteomyelitis of the trochanter. In 2 of these cases there was healing by first intention, sinuses developed in 6, but all healed within seven months after the operation.—*Tuberculosis of the great trochanter, B McMurray, Brit M J, September 27, 1947, no 4525 492—(R W Clarke)*

**Role of Pleura in Pneumonectomy**—With the removal of a tuberculous lung and its visceral pleura, the parietal pleura left *in situ* not only loses its function and usefulness but becomes a source of serious postoperative complications. Infection of the remaining pleura during or following pneumonectomy is not uncommon. Accordingly, the effect of total pleurectomy on the incidence of post-pneumonectomy complications, particularly empyema, was investigated. A review of 77 consecutive pneumonectomies showed that, following intrapleural pneumonectomy in 52 of these cases, bronchial fistula and/or empyema developed in 19. In addition, 8 patients had wound difficulties, 5 developed a bronchogenic spread, and 9 died. In contrast, following extrapleural pneumonectomy with removal of all or nearly all of the parietal

pleura in 25 cases, a bronchial fistula developed in 2 and wound difficulty in one. There was no instance of empyema or spread and no death occurred. The extrapleural approach in these cases was selected for technical reasons, principally the presence of encapsulated empyema or pleural symphysis. The general care and technique were identical with that for intrapleural pneumonectomy, the only variation being the complete or practically complete removal of the parietal pleura at the time of pneumonectomy. It is possible that the future treatment of bronchopleural fistula and empyema will consist primarily of extensive pleurectomy followed, if necessary, by bronchoplasty and thoracoplasty.—*The role of the pleura in intra and extrapleural pneumonectomy. Follow-up of seventy-seven consecutive cases, I G Tchertkoff & I A Selkoff, Quart Bull, Sea View Hosp, October, 1947, 9 277—(K T Bird)*

**Early Intrapleural Pneumonolysis**—At the Turunien Sanatorium, Finland, during 1945 and 1946 the aim was to perform all intrapleural pneumonolyses within one month after the induction of pneumothorax. Some had to be postponed when there was an accumulation of cases. Of 174 cases during 1946, pneumonolysis was attempted in 74 per cent before the fortieth day. In 14 cases, the procedure was done within two weeks. A complete severance of adhesions was possible in 75 per cent of the cases when intrapleural pneumonolysis was performed within one to five weeks after the induction of pneumothorax, compared to 55 per cent when the procedure was delayed for two or more months. Early pneumonolysis did not result in more complications but, rather, reduced the total incidence of febrile effusions and of intrapleural bleeding. The length of the sanatorium stay was reduced also.—*Optimum time for intrapleural pneumonolysis, S Anttila, Acta tuberc Scandinav, 1947, 21 274—(K T Bird)*

**Tuberculin Sensitization**—An attempt has been made to solve the ancient, controversial,

but important problem of whether tuberculin tests can produce a sensitivity to the substance in nontuberculous individuals. Eleven infants were found to be negative by Mantoux test to 1:100 dilution of O.T. They were then kept in isolation and Mantoux tests were repeated at about 48 hour intervals. From 11 to 60 tests were done on each infant during periods of one to six months, 2 individuals had small areas of erythema (on one and three occasions) with subsequent negative tests. Twelve infants were similarly tested with tuberculin patch tests. From 8 to 29 tests were done during periods of one to six months, 3 individuals had from one to three questionable reactions followed by repeated negative tests. It can be concluded that studies which require repeated tuberculin tests are safe from the hazard of lasting sensitivity from the tests.—*Nonsensitization to repeated tuberculin tests*, J. Schwartzman, M. Schneider & M. E. Crusius, *J. Pediat.*, December, 1948, 33:746—(W. H. Oatway, Jr.)

**Complications of BCG Vaccination**—Vaccination with BCG by the subcutaneous route is known to be followed sometimes by the formation of nodules and fistulous abscesses which may last for several months and which heal in the manner of cold abscesses. Little has been published about the complications of BCG vaccination by Rosenthal's intradermal technique. In a few patients vaccinated intradermally, however, following types of reactions have been observed: (1) local reactions of minor consequence at the site of vaccination, (2) lymphadenopathy in the regional nodes of the vaccination site, (3) distant lymphadenopathy of the mediastinal, inguinal, or supraclavicular nodes. The local reactions consist of macules, papules, and single or multiple abscesses ranging in size from that of a millet seed to that of a small marble. These suppurate and heal with scarring. The regional reactions consist of the enlargement of one or more axillary lymph nodes which may reach the size of a pigeon's egg and contain more than 10 cc. of pus. They generally suppurate and form fistulas which run a chronic course, usually of several months'

duration. When they heal, the scar has the classic scrofulous character. These lymph node enlargements appear at any time from fifteen days to eight months after vaccination and are not accompanied by any systemic reactions. The pus obtained from the lesions is like that of a cold abscess and in some cases may contain acid-fast bacilli. In most cases, none can be found. In 2 of the 12 cases cited by the authors, mediastinal, inguinal, and supraclavicular lymph node enlargements occurred. The mediastinal enlargement was easily demonstrated in the chest roentgenogram.—*Las complicaciones ganglionares supuradas de la vacunación BCG*, Rosenthal, P. Cantonnet Blanch, H. Cantonnet Blanch, and A. Pérez Scremini, *Rev. de tuberc. d. Uruguay*, June, 1948, 16:85—(F. Pérez-Pina)

**Tuberculosis and Sarcoidosis**—In discussions about the correlation between sarcoidosis and tuberculosis, cases have been cited in which the sarcoid manifestations are said to have regressed markedly during the development of chronic tuberculosis. Critical study of the literature shows that only a few cases of this nature have been observed and regression of the cutaneous sarcoid lesions during the development of tuberculosis is not the rule. A woman with extensive sarcoid lesions of the skin and osseous system was followed for five years. No regression of the sarcoid lesions was observed although she had gradually progressive, bacillary, cavernous, pulmonary tuberculosis with associated tuberculous spondylitis and probable tuberculosis of the knee during this time. The coexistence of these manifestations of typical sarcoidosis and typical tuberculosis during this long period suggests that these are two separate diseases.—*Progressive Boeck's sarcoid associated with protracted destructive tuberculosis*, R. Th. Björnstad, *Acta tuberc. scandinav.*, 1948, 22:142—(K. T. Bird)

#### CLINICAL STUDIES, NONTUBERCULOUS DISEASES

**Pulmonary Eosinophilosis**—Pulmonary eosinophilosis is a clinical condition char-

acterized chiefly by cough, paroxysms of dyspnea, and elevation of the white blood count with relative and absolute eosinophilia. Frequent systemic manifestations are fever, loss of weight, and lassitude. The literature contains 685 cases answering this description which were reported under many different titles. Most were reported from India and Ceylon and a few from other countries. All ages from one to 62 years were represented with the highest incidence from 20 to 40 years. There was a preponderance among males but the occupation of the patient was irrelevant. Mites were found in the sputum of some, there is some question as to the etiological significance of this finding. There were no autopsies. Clinically, there are 2 types: acute and chronic. The acute type begins abruptly with fever and cough as in pneumonia. The signs are those of bronchitis, with or without consolidation. In 25 per cent, the chest becomes clear in four to six weeks. The remainder enter the chronic phase. The chronic type, which is more frequent, either begins insidiously or is a residual of the acute type. It lasts for months or years with remissions or exacerbations. At first there is a nonproductive cough and mild fever, after one month, scanty expectoration appears. Later there is breathlessness and, less often, expiratory dyspnea. The fever lasts one to two months and the respiratory symptoms one year or more. The sputum often contains eosinophils. The spleen is enlarged in 50 per cent. The total white blood count ranges from 12 to 80 thousand with 20 to 80 per cent eosinophils. There is a high titer of cold agglutinins and a positive Wassermann or Kahn test is obtained in some. Roentgenograms show disseminated mottled shadows throughout all or parts of the lungs, later only increased markings remain. The differential diagnosis includes helminthiasis, asthma, and Löffler's syndrome. In asthma the white blood count is rarely elevated, roentgenograms are negative, and arsenicals give no relief. Löffler's syndrome is much milder and shows no constitutional symptoms. Arsenicals are specific therapy for pulmonary eosinophilosis, less than 2 per cent fail to

respond. The treatment consists of eight weekly injections of 0.15 to 0.30 Gm of neoarsphenamine. The author reports 207 cases, of which 11 were acute and 186 were chronic, with an abrupt onset in 22. Smears and cultures of the sputum were negative but mites were found in 21 cases. This finding was considered to be incidental, the balance of evidence favoring infection as the etiology. The Wassermann test was positive in 65 cases (32 per cent). The eosinophilia fell as treatment was given but improvement in other respects was more rapid. The first injection of the arsenical often caused an increase in eosinophils and an exacerbation of symptoms.—*Pulmonary eosinophilosis, V Viswanathan, Quart J Med, October, 1948, 17: 257—(A G Cohen)*

**Histoplasmosis**—About 100 cases of histoplasmosis have been reported, this report adds 10 cases from the Kansas City area. Five cases were fatal, 2 apparently have recovered. Seven patients were sensitive to a skin test with histoplasmin and 7 showed positive complement fixation reactions. Pulmonary infiltrations were noted in 9 of the cases, in 2 of which the lesions were of a miliary type. In 2 cases coexistent tuberculosis was demonstrated. A third case had Hodgkin's disease, proved post mortem by microscopic and cultural examination to be complicated by histoplasmosis. It is of interest that *Histoplasma capsulatum* was isolated by culture from the gastric contents of 4 patients.—*A report of ten proved cases of histoplasmosis, I Bunnell, M Furcolow, Pub Health Rep, March 5, 1948, 63: 299—(S Hadley)*

**Honeycomb Lungs**—A variety of cystic disease of the lungs is described in which thin-walled cysts up to 1.0 cm in diameter are distributed uniformly throughout the substance of both lungs. Sixteen cases were seen, of which 6 had systemic disease. The outstanding clinical features were spontaneous pneumothorax, often bilateral, and right heart failure. One case had xanthomatosis as did 3 of those reported in the literature. Pulmonary xanthomatosis is not rare. If

healing occurs, the lipoid cells are replaced by diffuse interstitial fibrosis and, in a few, cystic disease results. Biliary cirrhosis was seen in 2 cases. Tuberosus sclerosis was noted twice, about 10 cases were found in the literature. There were 2 cases with pituitary disorders. The remaining 10 cases had no systemic disease. The age at onset ranged from 7 to 55 years, the time from onset to death was one to six years. The patients were mostly males. Spontaneous pneumothorax occurred in 8 cases, and was bilateral in 5 of them. In 8 there was progressive dyspnea, 4 died of cor pulmonale within two years. Radiographically, there was a fine to coarse reticular pattern. The cystic spaces were more conspicuous when a pneumothorax was present. Tomograms in 4 cases demonstrated the honeycombing. Bronchography was done in 4 cases, the iodized oil did not enter the cysts. Histologically, there was interstitial fibrosis with no evidence as to cause. The cystic changes very likely are secondary to mechanical factors in acquired disease. The underlying disease is probably inflammatory, though this is not proved.—*Honeycomb lungs*, N Oswald & T Parkinson, *Quart, J Med*, January, 1949, 18:1—(A G Cohen)

**Pulmonary Embolism**—Pulmonary embolism, but not thrombosis, rarely occurs in children, 29 cases have been reported as occurring at ages less than fifteen years. The case of a boy who died suddenly at the age of nine years is reported. He had recovered from two episodes of pulmonary illness during the previous seven and one-half months during which time he had also had transient symptoms in the abdomen, one inguinal area, and both legs. Autopsy showed a massive new pulmonary embolism, signs of an older minor embolus and infarct, and partially organized thrombi in the inferior vena cava and common iliac veins. The rarity of peripheral thrombophlebitis in children is emphasized.—*Pulmonary embolism in childhood*, G F Steenson & F L Steenson, *J Pediat*, January, 1949, 34:62—(W H Oatway, Jr)

**Sarcoidosis**—The authors have used calciferol and dihydrotachysterol 50,000 to 300,000 units daily. Patients with sarcoidosis do not tolerate calciferol as well as patients with lupus vulgaris, and the more extensive the disease, the more severe are reactions. Early toxic symptoms consist of anorexia, nausea and vomiting, malaise, weakness, and dizziness. Dihydrotachysterol has been used in a dosage of 3.75 mg daily for three days to be followed by 1.25 or 0.625 mg daily for several months. Dihydrotachysterol is tolerated much better than calciferol, but eventually may give rise to the same symptoms.—*Sarcoidosis. III. A review*, A C Curtis & R H Grekin, *M Clin North America*, January, 1949, 31—(B Hyde)

**Primary Pneumonitis**—A five months old baby became ill with sneezing, cough, and fretfulness as the main symptoms. Both parents had a mild upper respiratory infection several days prior to the onset of the baby's illness. The baby recovered after being febrile for several days. Pharyngeal smears from the patient and from both parents showed characteristic cytoplasmic inclusion bodies. Subsequent smears made from the patient and from the father showed a decreasing incidence of cells with inclusions during a period of ten days.—*Primary pneumonitis in infancy*, J M Adams, J A M A, December 18, 1948, 138:1142—(H Abeles)

**Dual Fungous Infection**—The case of an eight year old boy who had a fatal infection with two fungi is presented. The child had pneumonia twice before the age of two years, a ringworm-like skin involvement of four years' duration from which *Candida albicans* was cultured after an exacerbation, and 4 pneumonic attacks in the fourteen months prior to hospitalization. Roentgenograms then showed soft nodular densities extending out from the hilar regions, much larger on the right. The sputum was positive for the same fungus. Skin test by an autogenous antigen was mildly positive, desensitization attempts

were followed by a clinical exacerbation. The urine culture was positive. Meningitis supervened and both *Candida albicans* and *Cryptococcus neoformans* were found in the spinal fluid and urine for 48 hours before death. Necropsy showed a generalized dissemination of the infection with cultures of various tissues irregularly positive for the two organisms — *Candida albicans* and *Cryptococcus neoformans* occurring as infective agents in an eight-year-old boy, C. Spicer, W. O. Hall, & J. F. Kessel, *J. Pediat*, December, 1948, 33: 761 — (W. H. Oatway, Jr.)

**Histopathology of Bronchiectasis**—Fifty human lungs that had been resected at the Mayo Clinic because of bronchiectasis were carefully sectioned, examined microscopically, and compared with sections of tissues from animals suffering from Jigizekte and chronic progressive pneumonia. In bronchiectasis the pulmonary alveoli commonly had a visible continuous lining of cells. These cells were derived from bronchial epithelial cells or from the pericapillary cells of the alveolar wall. The latter origin was far more frequently encountered than was the former. The appearance of the cells of alveolar origin differed markedly from that of the cells of the bronchial origin. In addition, cells of alveolar origin were frequently phagocytic after they had assumed a typical epithelium-like structure and arrangement. Although no conclusions were drawn regarding the endodermal or mesenchymal nature of the lining cells of the alveoli origin, it was conjectured that their parent cells also gave rise to the alveolar phagocytes. *Pulmonary alveoli linings in bronchiectasis*, C. F. Watts & J. R. McDonald, *Arch. Path.*, June, 1948, 45: 742 — (E. Bogen)

**Pulmonary Emphysema**—Pulmonary emphysema is difficult to diagnose by physical and roentgenologic examination. With the appearance of dyspnea and fatigue in chronic pulmonary or cardiac disease, a diagnosis of emphysema is frequently improperly made. Inasmuch as pulmonary emphysema is a functional disease due to interference with the

interchange of oxygen and carbon dioxide between the alveolar air and the blood, a diffusion test designed to measure the efficiency of this interchange can confirm or rule out emphysema of the lung. Without this diffusion test it is most difficult to state whether or not emphysema of the lung is present even when severe dyspnea exists. Dyspnea most frequently is caused by marked reduction in pulmonary ventilatory function. Several documented case records are reported to demonstrate that marked reduction in pulmonary ventilation can exist and emphysema of the lung not be present. Overdistention of a lung can exist for a long time without the development of pulmonary emphysema. A lung may hypertrophy and remain so for many years without loss of ventilation or diffusion functions. An hypertrophied lung may increase its ventilatory function through having been hypertrophied and overdistended for many years. The presence of emphysematous blebs or bullae in the lungs does not necessarily imply that the lungs are emphysematous unless there is functional impairment of pulmonary diffusion of oxygen and carbon dioxide. (Author's Summary)—*A new approach to the understanding of pulmonary emphysema. A method of determining emphysema of the lungs*, G. G. Ornstein, *Quart. Bull., Sea View Hosp.*, April, 1947, 9: 89 — (K. T. Bird)

**Bullous Emphysema with Infection**—Apparent cavitation was demonstrable on chest roentgenograms in 12 of 20 cases of primary atypical pneumonia seen during 1947. Two patients developed foul sputum for a short period and in 2 an atypical pulmonary abscess occurred. In 2 other cases the diagnosis of lung abscess was based on roentgenologic evidence of rarefaction, although the patients had no fever and no sputum. In all cases there was only a mild reaction about the cavities. It seemed unlikely that these were instances of ordinary lung abscess with dissolution and excavation of parenchymal tissue. However, an incomplete blocking of the bronchial branches by exudate or inflammatory changes

during primary atypical pneumonia may give rise to emphysematous bullae which resemble rarefaction in the chest roentgenogram. Superimposed anaerobic infection of these bullae may occur with the development of the clinical picture of putrid lung abscess—*Development of putrid pulmonary abscess in emphysema-bladders in primary atypic pneumonia*, M Ch Ehrstrom, *Acta med Scandinav*, 1948, 129 578—(K T Bird)

**Acute Lung Abscess**—The treatment of acute abscess of the lung by postural drainage, transthoracic injection of sulfonamides and penicillin, bronchoscopic aspiration, endobronchial catheterization, and nebulization offers a maximum of 30 per cent cures with a high mortality from residual bronchiectasis and fibrosis. The tendency of the process to spread and its marked toxicity demand early surgical external drainage. Four cases of acute lung abscess have been treated by external minimal drainage, intracavitary aspiration, and penicillin. This was given by concomitant instillation into the cavity and by intramuscular injection. The technique employed was (1) aspiration of pus from the abscess under fluoroscopic control, (2) lipiodol injection into the cavity to outline its inferior limits, (3) roentgenography, (4) drainage under local anesthesia using a 0.5 cm incision and introducing the trocar of a Coryllos thoracoscope through a thin layer of relatively avascular pulmonary tissue, (5) passage through the trocar of a flexible catheter which was secured to the chest wall, (6) continuous aspiration for 48 hours and then intermittent suction, alternating with injections through the catheter of 100,000 units of penicillin every 24 hours for five to ten days. Intramuscular penicillin, sulfonamides, liver, and vitamin C were also administered. Roentgenograms were taken every 48 hours. The aspirations were discontinued if they produced a hemorrhagic discharge or if the secretions disappeared with the loss of a fluid level and reduction in the size of the cavity—*Tratamiento del absceso agudo del pulmón por drenaje externo a mínima, con*

*aspiración endocavitaria*, J M Casal, *Rev de tuberc, d Uruguay*, March, 1948, 16 24—(F Pérez-Pina)

**Putrid Lung Abscess**—At the Harlem Hospital in New York City, spontaneous recovery from acute putrid abscess of the lung has been noted only in 11 per cent of 70 patients. Twenty-one patients with the acute disease have been treated with penicillin and sulfadiazine. Sulfadiazine alone has been found to be ineffective but it was hoped that it would act synergistically with penicillin, particularly against the perifocal pneumonitis. The sodium salt of penicillin was administered intramuscularly in doses of 40,000 units every three hours. The dose was increased if a prompt response was not obtained and several patients required 100,000 units every three hours. Sulfadiazine was given orally in the usual doses. Therapy was continued until all clinical and roentgenologic evidence of disease had disappeared. Nineteen of the 21 patients recovered completely. One patient died of a brain abscess although the pulmonary disease was cured, one patient left the hospital before treatment was completed. The average duration of treatment required to produce a remission of distressing symptoms and fever was six days (range from 2 to 35 days). An average of 42 days (range from 18 to 78 days) of treatment elapsed before the roentgenograms appeared normal. There were two recurrences, one in a severe epileptic and one in a severely alcoholic patient. The therapy was equally effective for small or large cavities and the authors believe that the size of the cavity is primarily determined by the degree of local obstructive emphysema rather than tissue necrosis. This type of treatment does not cure chronic putrid lung abscesses but in 8 of 10 patients the disease was improved and they were considered better candidates for surgical therapy. In view of the results obtained with drug therapy, the practice of early surgical drainage of acute putrid lung abscess must be revised—*The treatment of acute putrid lung abscess with penicillin and sulfadiazine*, B P Stuelman

and J. Kaveri, *Ann Int Med*, February, 1949, 30 525—(H. H. Nayer)

**Endothelioma of the Pleura**—The clinical features and the differential diagnoses of 10 cases of endothelioma of the pleura are discussed. The average age was 50 years, and death usually occurred within four to six months. The most important clinical sign is the rapid development of a hemorrhagic exudate which shows a marked tendency to reform after drainage. The strain on the pulmonary circulation always causes right ventricular hypertrophy with dilatation and corresponding electrocardiographic changes. Pronounced dyspnea develops, a secondary hypochromic anemia occurs regularly, and the sedimentation rate is increased. The Weltmann reaction shows a shift to the left. (Author's Summary)—*Zur Klinik der sogenannten Pleuraendotheliome (Mesotheliome)*, K. Kaiser, *Schweiz. Ztschr. Tuberk.*, 1948, no. 4 189—(E. Dunner)

**Pulmonary Adenomatosis**—Pulmonary adenomatosis represents about 5 per cent of all lung tumors, occurring in women more frequently than in men (ratio 3:2). The human disease resembles morphologically the pulmonary adenomatosis of sheep (Jagsiekte) which is thought to be caused by a filterable virus. Efforts to isolate a virus from the human cases have not been successful, the evidence seems to indicate that this disease is a specific response to certain nonspecific irritants. This response is hyperplastic and eventually causes death by extensive involvement of the lung parenchyma or by the development of truly malignant properties. Grossly pulmonary adenomatosis usually resembles the stage of gray hepaticization in pneumonia nodular, consolidated areas, somewhat like noncaseating miliary tuberculosis, have been described also. A primary bronchial focus has never been demonstrated. Noniliated cuboidal or columnar cells line the alveolar walls which are otherwise unaffected. The cytoplasm of these cells is eosinophilic, granular, or somewhat foamy. Bronchio-

pneumonia often obscures the condition. Although microscopically identical with so-called "alveolar cell carcinoma," pulmonary adenomatosis differs from carcinoma in that it usually does not metastasize. Two cases of extension have been reported, however, and metastasis has occurred in Jagsiekte of sheep. It is likely that adenomatosis of the lungs is a relatively benign variant of the "alveolar cell carcinoma" and is capable of developing all the characteristics of malignancy. There are no distinguishing clinical features of pulmonary adenomatosis. Each of the authors' 3 cases presented unusual findings. The findings in one case suggest a bronchogenic origin for the disease. In another case there was malignant proliferation of the cells of the adenomatous process. The nature of the cuboidal epithelium lining the air sacs and the loss of normal pulmonary architecture are unusual variations of the disease in the third case.—*Pulmonary adenomatosis. A report of three cases*, G. W. Drymalski, J. R. Thompson, & H. C. Swancy, *Am. J. Path.*, September, 1948, 24 1033—(J. S. Woolley)

**Cytological Examination of Sputum**—Sputum specimens of 1,600 patients were examined cytologically for cancer cells by the method of Dudgeon and Wrigley. Positive results were obtained in 150 cases. Normal and abnormal cells are described in detail. Statistically, examination of the bronchial secretions was no better than that of the sputum, however, examination of one supplemented the other. Of the 150 cases with positive findings, a final diagnosis of cancer was made in 145. In 3, the suspected condition was found to be noncancerous. In the other 2, the diagnosis of cancer was suspected but not proved. Bronchoscopy was performed for 114 of these cases. Positive biopsies were obtained in 66, negative biopsies in 31, and no gross abnormalities were seen in 17. In the other 32 proved cases of cancer, bronchoscopy was not done, the diagnosis having been proved in other ways. Surgery was done in 58 cases including 31 with a positive and 25 with a negative bronchus biopsy. The con-



dition was operable in 24, including 15 with positive and 9 with negative biopsies — *Carcinoma cells in sputum and bronchial secretions*, L B Woolner & J R McDonald, *Surg, Gynec & Obst*, March, 1949, 88 273 — (A G Cohen)

#### ANTIMICROBIAL THERAPY

**Para-aminosalicylic Acid** — Para-aminosalicylic acid (PAS) was discovered in the course of investigations of the metabolism and growth of tubercle bacilli. In 1940 and 1941, Bernheim showed that salicylic and benzoic acid increase the oxygen utilization and carbon dioxide formation of tubercle bacilli. Salicylic acid exerts this action only on pathogenic tubercle bacilli and is thought to act as a co-factor in the oxidative process. Lehman obtained identical results and noticed that salicylic acid exerts a powerful bacteriostatic action on tubercle bacilli in synthetic media. In an attempt to find a compound that competes with salicylic acid in the oxidative processes of tubercle bacilli, he investigated 60 derivatives of salicylic and benzoic acid. Para-aminosalicylic acid showed tuberculostatic activity which is equalled by few compounds and approaches the activity of streptomycin, inhibiting virulent human tubercle bacilli in a concentration of 1:2,000,000. The effectiveness of PAS in the treatment of experimental tuberculosis was quickly proved and it was found that the drug had a low toxicity. Clinical investigations established the dosage as 10 to 15 Gm daily in divided doses given over a period of months, one week of treatment alternating with one week without treatment. More than 100 patients with pulmonary tuberculosis were treated, 60 to 70 per cent showed good result initially. Results also are promising in renal tuberculosis and in the topical treatment of abscesses and empyema cavities with a 10 per cent solution of PAS or its sodium salt. The drug has not fulfilled its promise, however, in the treatment of miliary tuberculosis and tuberculous meningitis, perhaps because insufficient doses have been used — *P-Aminosalicylsäure in der Chemotherapie der Tuberkulose*, L Ragaz,

*Schweiz med Wchnschr*, April 10, 1948, 78 332 — (H Marcus)

**PAS for Tuberculosis** — A total of 30 cases of tuberculosis were treated with para-aminosalicylic acid (PAS). The drug was administered orally for four days followed by a three day pause. The treatment was continued over a period of several months, the daily dose averaging 12 to 15 Gm. Definite beneficial effects on temperature elevation, amount of sputum, number of tubercle bacilli, and sedimentation rate were observed especially in the exudative forms. In 5 cases of tuberculous empyema complicating intra- or extrapleural pneumothorax, PAS was used locally. After several weeks of treatment, growth of tubercle bacilli on culture was inhibited in each case — *Die Behandlung der Tuberkulose mit Para Amino Salicylsäure*, H Steinhilber, *Schweiz Ztschr Tuberk*, 1948, no 6 391 — (E Dunner)

**Para-aminosalicylic Acid for Tuberculosis** — Para-aminosalicylic Acid (PAS) and sodium PAS are being used extensively in Switzerland for chronic pulmonary tuberculosis with cavities and for tuberculosis of the bronchi, larynx, cervical nodes, urinary tract, and middle ear. It also is used intrapleurally for empyema. The drug is introduced directly into the cavity in daily doses of 2 cc of a 20 per cent solution. This is supplemented by 10 to 20 Gm daily given orally in divided doses. For bronchial lesions, 2 cc of 20 per cent solution are administered as aerosol, supplemented by 10 Gm daily by mouth. For otitis media, 2 to 3 drops of 20 per cent solution are used. In renal disease, 10 to 20 Gm are given orally each day. The drug is available in ointment and cream for use in external sinuses and ulcers. Sometimes sodium PAS is given intravenously. PAS also is used in conjunction with streptomycin — *PAS in Switzerland*, M Seiler, *Tubercle*, February, 1949, 30 45 — (A G Cohen)

**Lupus Vulgaris** — The treatment of cutaneous tuberculosis with calciferol frequently

leaves the patient with residual activity in the lesions. Five patients with lupus vulgaris were treated with calciferol until it ceased to be of benefit after a period of five months to a year. They were then treated with streptomycin in combination with calciferol. The lesions became inactive within six to nine weeks, suggesting a synergistic action of the 2 drugs. Two other patients were treated with streptomycin and calciferol for seven and eight weeks, respectively. They received 10 Gm of streptomycin and 100,000 units of calciferol daily. Both patients showed rapid and uneventful healing of the lesions—*Combined calciferol and streptomycin in lupus vulgaris, T Cornbleet, J A M A, December 18, 1948, 138 1150*—(H Abeles)

**Streptomycin Frugality**—Experience with penicillin and a consideration of Corper's conclusions from the use of streptomycin in animals have resulted in a program for treating certain types of tuberculosis in children. Smaller doses and less frequent injections than have ordinarily been prescribed are used. Treatment is given without interruption until the lesions are stable, the doses being reduced and the intervals increased as treatment progresses. It has been found that a solution containing 166 mg per cc can be used with comfort. A series of cases is reported in which such a routine was used. All of 13 cases were acute and febrile before treatment, 3 had milary disease, 6 had hilar gland lesions, and 4 had primary childhood type of tuberculosis. The milary cases were treated for two to four months and the others from four to six weeks. At the start 20 mg per Kg of body weight per day were given at intervals of four hours, the dose was decreased to 5 mg per Kg per day and the interval lengthened to twelve hours or even 48 to 72 hours in some cases by the end of the second week. All cases healed. A case is reported in detail to demonstrate the repeatedly unfavorable effects of discontinuous administration—*Streptomycin in tuberculosis of children. Treatment with less frequent injections and more concentrated solutions, D Hirschl, H Levy & A M*

*Latval, Arch Pediat, December, 1948 65 640*—(W H Oatway, Jr)

**Antihistaminic Drugs with Streptomycin**—Nausea and vomiting occur in some patients undergoing prolonged treatment with streptomycin and might be due to the same cause as the urticaria sometimes seen. In 4 patients severe toxic symptoms were abolished or considerably reduced when benadryl was given and returned when the medication was withheld. This response might have been due to the sedative effect of benadryl but, when 30 mg of phenobarbital was substituted, the nausea returned. The resumption of benadryl was followed by immediate relief. In 3 of the 4 cases, the nausea and vomiting were so severe that streptomycin therapy would have been discontinued but for the beneficial effect of benadryl in relieving the symptoms—*Antihistamine drugs in treatment of nausea and vomiting due to streptomycin, J R Bignall & J Crofton, Brit M J, January 1, 1949, no 4591 13*—(R W Clarke)

**Vitamin B Deficiency with Streptomycin**—Three patients who were receiving streptomycin for tuberculosis developed angular stomatitis and glossitis. These were relieved by the administration of niacin and riboflavin. Neither 15 other patients currently on the ward nor 154 patients treated during the year showed similar findings. Evidence is presented to show that streptomycin exerts a bacteriostatic effect on intestinal organisms which may be concerned in the assimilation of these vitamins—*A clinical report of three cases of vitamin B deficiency occurring during streptomycin therapy, J Sumner, Tubercle, March, 1949, 30 62*—(A G Cohen)

**Streptomycin for Pertussis**—Because strains of *H pertussis* were found to be sensitive to streptomycin *in vitro*, it was thought desirable to ascertain the efficacy of the drug in the treatment of whooping cough. A total of 11 children were treated. In 3 cases, two daily treatments were given consisting of inhalation of 50,000 units of nebulized streptomycin by means of a special helmet

In 3 cases, the treatments were given four times a day. In 3 cases, 200,000 units were given intramuscularly four times a day. In one case, both intramuscular and inhalation treatments were given. Streptomycin was not recovered from the blood or urine of any patient who received the drug by inhalation alone. The clinical course of the disease was not modified in any treated case—*Streptomycin in whooping cough*, H Schwabacher, R H Wilkinon & C W C Karran, *Lancet*, January 29, 1949, 2 180—(A G Cohen)

**Streptomycin for Pneumonia**—Respiratory infections may be caused by *Hemophilus influenzae* and in infants there are no typical clinical characteristics of the disease. Mortality in infants has ranged from 7 to 40 per cent, depending on what part of the respiratory tract is involved, despite the use of sulfonamides and antiserum. Three cases with a laryngotracheitis due to *H influenzae* were treated with streptomycin, all improved abruptly within twelve hours. Four cases of laryngotracheobronchitis due to the organism were treated with streptomycin, they improved within twelve hours and all recovered. No streptomycin-resistant strains were found. It is suggested that the drug be given to all young infants with laryngotracheobronchitis and continued until a nonsusceptible organism has been demonstrated—*Streptomycin in the treatment of Hemophilus influenzae laryngotracheobronchitis*, C O Terrell Jr & C S Hoar, *J Pediat*, February 1949, 34 139—(W H Oatway, Jr)

**Empyema**—The extensive use of penicillin in infections of the respiratory tract has reduced the frequency of pleural abscesses to 0.08 per cent or less in most series of cases. If pleural fluid appears, local treatment should be withheld until an attempt has been made to identify the infecting organisms. Penicillinase should be used in the laboratory to counteract the inhibitory effect of penicillin on the organisms if the agent already has been given. Streptomycin should not be employed unless there are absolute indications based on bacteriologic evidence. The early, vigorous, parenteral, and intrapleural use of penicillin

as soon as infected fluid appears in the pleura will abort the formation of a frank abscess in many cases. If frank, thick pus forms, however, surgical drainage or decortication with drainage should be employed—*Empyema*, B Blades, *J A M A*, November 27, 1948, 138 948—(H Abeles)

**Aureomycin for Atypical Pneumonia**—Thirteen patients with primary, atypical, nonbacterial pneumonia were treated with aureomycin. Detailed data of the clinical, laboratory, and serologic findings are given. Six patients had high titers of cold hemagglutinins and 9 patients had positive *Streptococcus MG* agglutination reactions. Treatment with aureomycin was begun on the second to twenty-first day of illness. The usual schedule of drug administration consisted of a "priming" dose of 100 to 250 mg every hour for 3 doses, followed by the same dosage every two hours until the patient became afebrile. Thereafter, the drug was given every four to six hours for two to five days (15 to 20 mg per Kg of body weight). Nine patients were afebrile within 24 hours after the institution of aureomycin therapy, 3 within 24 to 48 hours, while one patient did not become afebrile until 72 hours after treatment. Subjective clinical improvement coincided with lysis of the fever. There were no serious toxic manifestations although several patients complained of mild drowsiness—*Treatment of primary atypical nonbacterial pneumonia with aureomycin*, E B Schoenbach & M S Bryer, *J A M A*, January 29, 1949, 139 275—(H Abeles)

#### LABORATORY STUDIES

**Pleural Fluid Sugar**—The sugar content of the pleural fluid was determined in a series of 33 cases, the venous blood sugar being determined at the same time. The results suggest that a low concentration of sugar in the pleural fluid may be diagnostic of tuberculosis. Each of the 10 cases of tuberculosis had a sugar concentration below 39.5 mg per 100 cc, the average being 15.7 mg. It is felt that the finding of 30 mg per 100 cc or less should be diagnostic of tuberculosis while a concentration above 60 mg per 100 cc should eliminate

tuberculosis as the cause of the effusion — *Relationship of the pleural fluid sugar to pulmonary tuberculosis*, S M Gelenger & R F Wiggers, *Dis of Chest*, March, 1949, 15 325 — (E A Rouff)

**White Mouse in Tuberculosis** — The white mouse is extremely useful in experimental tuberculosis. Following intravenous injection of a standardized inoculum of tubercle bacilli, the severity of the infection can be measured by the length of the survival time and the extent of macroscopic dissemination. With this method doses of 0.06 to 1.0 mg of virulent tubercle bacilli yield easily reproducible results in full-grown mice. They die within three weeks. Both sexes appear equally susceptible but the infection has a more irregular and prolonged course in immature mice. The size of the animal, the simplicity of the intravenous technique of infection, and the small amounts of drugs that are required for therapeutic evaluation facilitate extensive experimental investigations. The only obvious disadvantage is the marked susceptibility of the white mouse to intercurrent infections, particularly those with the *Salmonella* group of bacilli — *The white mouse in experimental tuberculosis*, B Swedberg, *Acta tuberc Scandnav*, 1948, 22 260 — (K T Bird)

**Bacillary Wax and Delayed Hypersensitivity** — Studies of delayed hypersensitivity to tuberculin have demonstrated that (1) the isolated protein antigen of the tubercle bacillus cannot induce tuberculin hypersensitivity but the entire organism can, (2) the "wax" of the bacillus when administered with protein causes a delayed response. Picryl chloride alone induces delayed hypersensitivity only when administered through the skin but, if tubercle bacilli are injected with picryl chloride by another route, delayed hypersensitivity to the chemical ensues. Picryl chloride is a simple hapten which combines spontaneously with protein to form a complete antigen in the tissues. The "wax" of the tubercle bacillus may determine the delayed response to picryl chloride as it determines the similar response to tuberculo-protein. To test this thesis, groups of

guinea pigs were treated with picryl chloride by applying it to the skin or by injecting it intracutaneously, subcutaneously, and intraperitoneally. The chemical was injected intraperitoneally with a water in oil emulsion or with the "wax" from tubercle bacilli. All animals later received both contact and intracutaneous skin tests with weak solutions of picryl chloride. A few animals, especially those sensitized by placing the chemical on or into the skin, later reacted moderately to the contact and intradermal tests. Thirteen of the 15 animals which received picryl chloride with "wax" developed marked delayed hypersensitivity to both tests after only one treatment. This sensitivity was not increased by repeated injections and it persisted for 164 days. The high degree of hypersensitivity appears to depend upon a specific property of the "wax", a simple adjuvant activity is unlikely because the water in oil emulsion did not cause the same responsiveness to the antigen. Further tests showed that the reaction bore no relationship either to the occurrence of a humoral antibody or to an immediate hypersensitivity of the anaphylactic or Arthus type. Passive transfer of the hypersensitivity was impossible. The so-called "heteroallergic" phenomena in tuberculosis may appear because the bacillary "wax" causes tissues to respond with tuberculin-type reactions to various antigenic substances. The moderate, delayed response to picryl chloride introduced along by way of the skin, may be due to a tissue lipid with properties similar to those of the bacillary "wax" — *The role of the "wax" of the tubercle bacillus in establishing delayed hypersensitivity I. Hypersensitivity to a simple chemical substance, picryl chloride*, S Raffel & J E Forney, *J Exper Med*, October 1, 1948, 88 485 — (J S Woolley)

**Virulence Variations of BCG** — Four strains of BCG which had been cultivated differently for many years were studied under standardized conditions. It was found that the virulence of these strains was rather uniform regardless of whether they had been cultivated exclusively on bile-potato medium, on bile-potato medium and glycerine-potato medium

alternately, or exclusively on Sutton's medium. For some BCG strains at least, it is apparently immaterial whether they are maintained on a medium containing bile. Some of the variation in the action of BCG may be due to differences in the technique of preparing the vaccine rather than to changes in virulence. The rate of growth of a culture and the stage of growth at which it is collected are significant factors in this respect. Because a standardized technique is so important, an international BCG standard would be helpful. Preliminary studies of BCG vaccine with a freeze-drying technique give promise of a basis for the latter—*Variations in the Virulence of BCG, J Bøe, Acta tuberc Scandinav, 1948, 22 125*—(K T Bird)

**Rapid Streptomycin Sensitivity Test**—The usual methods of determining the streptomycin sensitivity of tubercle bacilli make results available to the clinician only after six to eight weeks. A more rapid technique has been elaborated in the Institute of Hygiene, Lausanne, Switzerland. A part of each specimen is mixed with an equal amount of a streptomycin solution containing either 10 or 10  $\gamma$  per cc. These mixtures are inoculated directly on solid Löwenstein medium. Three series of tubes are incubated: (1) specimen without streptomycin, (2) specimen with streptomycin solution of 10  $\gamma$  per cc, (3) specimen with streptomycin solution of 10  $\gamma$  per cc. The results can be evaluated after two weeks. The strain is considered resistant if it grows in both streptomycin dilutions. A strain is considered at the lower limit of resistance if it grows only in 10  $\gamma$  per cc. This method admittedly gives only a rough estimate of the streptomycin sensitivity and should always be followed by the usual sensitivity determinations in liquid media—*Nouvelle méthode de titration de la streptomycino-résistance du bacille tuberculeux, P Haduroy et W Rosset, Rev de la tuberc, 1948, 12 834*—(V Leites)

**Plastic Irritants**—Certain synthetic plastic materials have the ability to incite fibrosis. Cellophane and polythene are such irritants

although the effect of the latter varies with its quality. The experimental production of pleural and pulmonary fibrosis has been tried in a dozen dogs using the two plastics. A sheet of plastic was wrapped around portions of one lung at pleurotomy after which the effects were noted clinically at the end of three and six months. Both plastics produced thickened pleura, collapse of the chest wall and lung, and some fibrosis of the lung. Cellophane tends to produce a fulminating type of reaction but the changes are compatible with life and health. The effect of the films was variable, since the reaction is due to plasticizers used in manufacture and the film is the vehicle of the chemical on its surface. The utility and effect of the methods in human tuberculosis is conjectural but it could be tried for the production of adhesions and to obliterate blebs and fistulae—*Experimental pulmonary collapse, J L Southworth, Ann Surg, January, 1949, 129 85*—(W H Oatway, Jr)

**Tissue Distribution of PAS**—The distribution of para-aminosalicylic acid (PAS) in various tissues was studied by means of fluorescence microscopy. Specimens were fixed in liquid air and dried *in vacuo* before being embedded in paraffin and sectioned. No staining was performed. In ultra violet light PAS has a strong, green fluorescence. It was found that PAS accumulates in elastic fibres but not in collagenous tissue so that a normal lung absorbs relatively large quantities of this drug. However, the quantities are smaller in tuberculous cavities where the elastic fibres are severed and partially destroyed—*The distribution of para-aminosalicylic acid in the tissues, K Aln & S Helander, Acta tuberc Scandinav, 1948, 22 283*—(K T Bird)

**Insulin Tolerance in Amyloidosis**—The insulin tolerance test is shown to be abnormal in amyloidosis. This abnormality consists of an increased resistance to insulin and an impaired response to hypoglycemia. It is suspected that this response is the result of hepatic dysfunction. The cases studied also showed an abnormal retention of bromsulphalein and significantly positive cephalin-

cholesterol flocculation tests in addition to Congo red absorption and hepatomegaly. The test responses were similar to those found in other types of liver disease and to those elicited in cases of portal cirrhosis tested concurrently (Author's Summary)—*The insulin tolerance test in amyloidosis*, S London, *Quart Bull, Sea View Hosp, April, 1947*, 9 187—(K T Bird)

#### PUBLIC HEALTH AND EPIDEMIOLOGY

**Loss of Tuberculin Sensitivity**—A series of 7,500 school children from 4 to 20 years of age was tested with tuberculin. Children under 14 were tested by percutaneous methods, the intracutaneous method was used for older subjects. All were observed for periods of one to seven years, 2 to 10 tests being made in each case. When the reactions became negative, control tests were made eight to fifteen days later. Of the 7,500 children, 2,315 showed positive reactions when first tested, 320 of them later became negative reactors. Of 496 children 4 to 10 years of age, 175 (35 per cent) became negative reactors, of the 1,338 children 11 to 15 years of age, only 128 (9.5 per cent) failed on subsequent tests to react to tuberculin. Of the 441 students 16 to 20 years old, 17 (3.8 per cent) became nonreactors. Attention is called to the fact that young children often have been removed from foci of infection. Acute tuberculosis is less frequent among them than among adolescents who are more exposed to reinfection. Reappearance of sensitivity to tuberculin after it has been lost is considered by the authors to be evidence of reinfection rather than of the persistent influence of primary infection—*Extinction spontanée des réactions cutanées à la tuberculine chez l'homme*, M Gillard & A LeCocq, *Acta tuberculosea Belgica*, April, 1948, 39 97—(A T Laird)

**Effect of Amount of Tuberculin**—A series of 109 apparently healthy individuals were subjected to 2 simultaneous Mantoux tests. Of the individuals, 94 had normal chest roentgenograms, 3 showed hilar adenopathy, and 9 had pulmonary calcifications. Each subject received 0.1 cc of a 1:5,000 tuberculin

solution at one site and 0.2 cc of the same dilution at a second site 10 cm away from the first. There was a negative reaction to the 0.1 cc injection in 33 per cent of the subjects and a negative reaction to the 0.2 cc injection in only 19 per cent. The positive reactions were generally stronger with the larger injections. Similar tests were conducted on 110 individuals using 0.1 cc of a 1:5,000 tuberculin solution and 0.2 cc of a 1:10,000 solution. The reactions obtained with these two injections were almost identical. Thus the amount of tuberculin rather than the volume of solution injected determines the results obtained. *Contribución a la práctica de la reacción de Mantoux*, A R Ginés, E Gould, & C R Talavera, *Hoya tsiol*, June, 1948, 8 117—(F Pérez-Pina)

**BCG in Adults**—The authors have administered BCG by the scarification route to 4 different groups of student nurses in Paris since 1942. In the first group 100 tuberculin-negative student nurses have been vaccinated since 1942. One of them developed serofibrinous pleurisy eighteen months after vaccination but recovered without further consequences. All of the other students have remained in perfect health. Some nonreactors in the same group refused vaccination. In 38 per cent of them, tuberculous manifestations have appeared, including erythema nodosum, serofibrinous pleurisy, tuberculous peritonitis, and active pulmonary tuberculosis. In a second group of nurses, 43 nonreactors have received BCG since 1943. None of them has developed any tuberculous manifestations during the following five years, whereas in the years preceding the use of BCG one case of miliary tuberculosis and 6 cases of primary tuberculosis had been observed. In a third group of student nurses, 50 have been vaccinated since 1944. Among them there has been one case of abscess due to BCG and this healed spontaneously. No other tuberculous incidents have been noted. A fourth group of student nurses have received BCG since 1945. Among the vaccinated persons there were 3 cases of transient mediastinal adenopathy with fever. From 1939 to 1945, before the use

of BCG, 21 of 116 nonreactors developed tuberculous manifestations, 3 of which were fatal—*L'extension de la prévention de la tuberculose par le BCG aux adolescents et adultes, A Courcoux, Presse med, June 12, 1948, 410*—(V Leites)

**Contact Control During Vaccination**—An individual is "vaccinated" with BCG only when a routine is observed which protects him from contact infection until the inoculation becomes effective. Proof of "vaccination" can be obtained only by the use of pre- and post-inoculation tuberculin tests. There is a definite difference between the terms "BCG inoculation" and "BCG vaccination", the inoculated individual must have had the required tuberculin tests to be considered vaccinated and to be usable in statistics. The report of Levine and Sackett of New York is vulnerable because of a failure to isolate infants during the inoculation period. They were aware of this fault, as shown by their follow-up study, but their objection to isolation is not valid. When isolation and control are used, the results show an eminent advantage. Control groups of unvaccinated persons are no longer available in Sweden since physicians consider it a dangerous experiment to withhold BCG inoculation and the law considers it criminal—*BCG inoculation and BCG vaccination, A Wallgren, Am J Dis Child, November, 1948, 76: 485*—(W H Oatway, Jr)

**Q Fever**—Q fever was first recognized in California in April, 1947. This study includes 300 cases that have been investigated in the Los Angeles area since September, 1947. A definite diagnosis was made either on the basis of recovery of *C burnetii* from the tissues in two fatal cases, from the blood of other acutely ill patients and the urine of convalescents, or on the basis of the complement fixation test. A total of 483 complement fixation tests were made, in general, the titers increased until the fourth week of illness and then tended to subside gradually over a period of years. Pneumonia was the initial diagnosis by physicians in over 100 cases and was noted in the roentgenograms of 97 of 115 cases. Chest pain, cough, and hemoptysis were

described. The cases occurred throughout a wide area at all seasons and over several years. The patients were predominantly males in the industrial age groups but their occupations were extremely diversified. In all, the epidemiological findings suggested 3 general hypotheses as to the modes of spread: (1) occupation in the dairy or livestock industries, (2) residence close to dairies or livestock yards, and (3) household use of raw milk. *C burnetii* was recovered from 40 of 50 specimens of raw milk collected from five dairies. However, no one of these possible modes of spread would account for more than one-half of the cases—*Q Fever studies in Southern California II. An epidemiological study of 300 cases, M Beck, J Bell, E Shaw, & R Huebner, Pub Health Rep January 14, 1949, 64: 41*—(S Hadley)

**Industrial Atmospheric Pollution**—Donora is a borough in Pennsylvania inhabited by 14,000 people. Its main industries are a zinc smelting plant, a steel and wire plant, and slag crushing plants. It is situated on a river along whose banks many heavy industries are located. There is very heavy river and rail traffic which adds to the pollution of the air. For four days last winter there was an exceptionally heavy fog. The following day deaths began to occur rapidly, reaching a total of 18 in 36 hours. All the victims were known to have had heart disease or asthma, their ages ranged from 52 to 85 years. Five hundred other people suffered from dyspnea and cough. On the second day, repeated samples of air were analyzed for sulphur dioxide, which is the most irritating of industrial gases. The first sample showed 0.54 parts per million, falling to 0.08 parts in five hours, at about which time the disaster began to abate. The situation on the previous day unfortunately is not known. The upper limit of safety for sulphur dioxide is thought to be 0.5 to 0.75 parts per million. These concentrations were approached, if not exceeded. Soluble sulfates were found to be present in a concentration of 0.2 mg per cubic meter—*The Donora disaster, J Shullen, Indust Med, February, 1949, 18: 70*—(A G Cohen)

# INFLUENCE OF TYPE OF DISEASE ON THE RESULTS OF THORACOPLASTY IN PULMONARY TUBERCULOSIS<sup>1</sup>

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## INTRODUCTION

Extrapleural thoracoplasty is a well established procedure in the surgical treatment of pulmonary tuberculosis. The late results, however, still include a significant number of failures for an apparently standardized operation. Unsuccessful results are generally ascribed to poor choice of patients, insufficient collapse of the diseased lung, or to complications resulting from the operation itself. But in spite of more careful selection of patients and greater refinements in operative technique, there has not occurred a significant improvement in the results in recent years. Whether or not the picture has changed significantly since the introduction of streptomycin is a matter to be decided in the future.

The following report is an analysis of the early and late results of thoracoplasty in 168 patients with pulmonary tuberculosis operated upon at the Triboro Hospital over a period of five years, and followed from two to six years since the completion of the operation. In this analysis particular emphasis has been placed on the type of disease treated. The patients were subgrouped according to the predominant clinico-pathologic feature of the disease as determined from their records and serial chest roentgenograms prior to the thoracoplasty. The results of the operation within the individual groups were then studied and compared. The data were also reviewed for the group as a whole to permit a comparison of the results in this clinic with those obtained in other clinics. It was hoped that an analysis of the results in the manner outlined might be fruitful in establishing more precise indications and contraindications in the use of thoracoplasty and the other surgical procedures, such as pulmonary resection, which are currently employed in the treatment of pulmonary tuberculosis.

## MATERIAL

From January 1941 until January 1946, extrapleural thoracoplasty was performed on 168 patients with pulmonary tuberculosis. The group included 107 males and 61 females and consisted of 153 white patients, 11 Negroes, 2 Chinese, and 2 Porto Ricans. Thoracoplasties performed for tuberculous empyema were excluded from the analysis. The operation was uniform throughout the series and consisted of the modern multi-staged, selective thoracoplasty. The number of stages and ribs resected depended upon the extent and location of the disease and the condition of the patient. The transverse processes were, as a rule, resected. An apicolysis was performed only in selected cases. Supplementary

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operations such as anterior stages and revisions were performed, when indicated, to close residual cavities

With the few exceptions to be noted later, the indication for thoracoplasty was the presence of cavitary pulmonary tuberculosis and tubercle bacilli in the sputum or gastric washings. In 5 patients the sputum became negative for tubercle bacilli prior to surgery but, because of poor family background and evidence of previous instability of the disease, thoracoplasty was considered advisable. Tomographic studies were done in almost every instance before and after surgery. Small cavities were occasionally discernible by tomography in the contralateral lung which were not detected in routine films. One hundred thirty-nine patients were bronchoscoped preoperatively. Pulmonary functional studies, including bronchspirometry, were performed in borderline cases, especially in the presence of bilateral disease or if there had been a history of contralateral

TABLE 1  
*Age Incidence*

AGE	NUMBER OF PATIENTS
15 to 20	7
21 to 30	55
31 to 40	59
41 to 50	34
51 to 57	13
Total	168

disease that had required collapse treatment. All patients over 40 years of age were examined by a cardiologist before operation. None of the patients received streptomycin, as the operations were performed before this antibiotic came into general use.

#### *Classification*

To permit a more accurate analysis of the factors entering into the results, the 168 cases submitted to thoracoplasty were divided into groups based on the predominant clinico-pathologic feature of the disease as determined by serial roentgenograms and the clinical course. The determining factor in this classification was not the size of the cavity, but rather the underlying pathology leading to cavity formation. Large, thin-walled cavities were therefore differentiated not because of their size but because they represent a definite pattern of pulmonary tuberculosis. The fate of pulmonary cavities depends largely on their bronchocavitary dynamics, that is, the degree of stenosis of the draining bronchi traversing the cavity wall and the elasticity of the cavity wall itself, whether atelectatic or fibrotic.

**Group I *Fibrocaceous tuberculosis*** This group was characterized by predominantly productive lesions, limited in extent, associated with small or moderate-sized cavities. Active disease had usually existed one to two years and appeared clinically stabilized at the time of surgery. This group yields the largest number of cases treated with thoracoplasty.

Group II *Fibroid tuberculosis* Pulmonary disease with marked fibrosis and retraction of the involved lobes associated with rigid cavities, bronchiectasis, and emphysema was included in this category. The disease had usually existed for many years.

Group III *Caseocavernous tuberculosis* A few patients were found to have a progressive, caseating form of tuberculosis. They were submitted to thoracoplasty with the hope that the operation might halt the progress of the disease.

Group IV *Tuberculosis associated with large thin-walled cavities* Patients whose lungs contained large, thin-walled cavities were included in this group. Small disseminated tuberculous foci usually surrounded the cavity. Multiple cavities occasionally were present. As a rule, the patients were in good health.

Group V *Tuberculosis and bronchiectasis* This group consisted of patients with upper lobe fibroid tuberculosis and lower lobe bronchiectasis. This type of lesion is widely classified as the "destroyed lung." The bronchiectasis was not necessarily tuberculous in nature.

TABLE 2  
*Extrapleural Thoracoplasty 168 Cases*  
*Pathologic Pattern and Extent of Diseases*

TYPE OF DISEASE	NUMBER CASES	DISTRIBUTION		
		Unilateral active		Bilateral active disease
		No Contra lateral Disease	Contralateral inactive	
I Fibrocaceous	117	37	60	20
II Fibroid	13	2	10	1
III Caseocavernous	5	2	3	0
IV Giant cavity	23	6	17	0
V Tuberculosis and bronchiectasis	6	3	2	1
VI Unexpandable lung	4	3	1	0
Total	168	53	93	22

Group VI *Unexpandable lung* Patients in this group had previously had pneumothorax treatment, which had resulted in an unexpandable lung due to stenosis of a major bronchus. Unexpandable lung due to a pleural membrane was not noted since patients with pleural complications were excluded from this survey. Actually, the unexpandable lung is a complication of therapy rather than a type of pulmonary tuberculosis.

In table 2 may be seen the distribution of the cases according to the above classification. One hundred forty-six patients were found to have unilateral active disease, 93 of whom had evidence of inactive tuberculosis in the contralateral lung. Twenty-two patients had bilateral active tuberculosis.

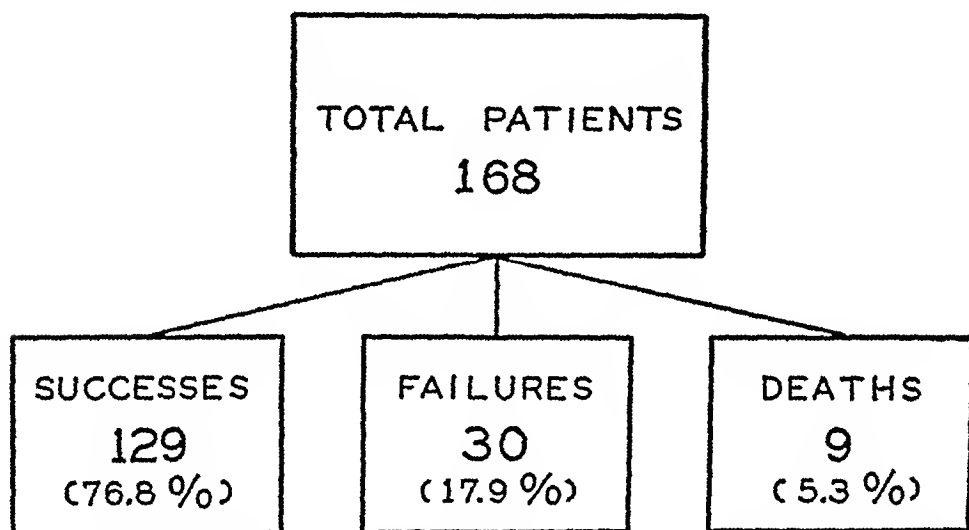
## RESULTS

### *Combined Groups*

*Immediate results* The immediate results for the entire series of cases are summarized in table 3. The early results were based on the status of the patients six to eight weeks after the completion of the thoracoplasty when they were usually transferred to the medical service for further convalescence. The oper-

ation was considered "successful" when (1) cavity closure was realized as determined by Bucky roentgenograms and tomograms, (2) sputum "conversion" was achieved on repeated sputum or gastric concentrates and cultures, and (3) respiratory function seemed adequate. Relative degrees of improvement were not classified. A thoracoplasty which failed to close the cavity and "convert" the sputum, or could not be completed because of a deterioration in the patient's status or as a result of respiratory insufficiency resulting from the operation, was considered a "failure." No case was classified as a failure, however, unless active disease was present following a thoracoplasty which could not be completed, or after attempts to control the disease by supplementary surgery, such as anterior stages or revisions, had failed. Thoracoplasty failures submitted to pulmonary resection were still classified as failures.

TABLE 3  
*Early Surgical Results*



As may be seen in table 3, cavity closure and sputum "conversion" were achieved in 129 (76.8 per cent) of the 168 patients submitted to thoracoplasty. Residual cavitation and/or persistently "positive" sputum were found in 30 patients (17.9 per cent). Nine patients did not survive the operation, a mortality of 5.3 per cent. The postoperative complications are analyzed in table 4. Wound infections occurred in 25 patients. Postoperative spreads of disease occurred in 19 patients. In 13 instances, this complication occurred on the operated side and in 6 on the contralateral side. The fatalities are analyzed in table 5.

*Late results.* A recent follow-up report was obtained in 141 of the 168 patients two to six years following the operation. Twenty-seven patients could not be traced. Patients who were not attending the Triboro follow-up clinic were traced by questionnaires sent to hospitals, chest clinics, or private physicians. In table 6 is shown the present status of the patients traced. To present a comprehensive survey of the results, the early as well as the late fatalities are included.

Of 111 patients followed, 89 (63.1 per cent) are clinically well, the disease arrested. Thirty-two patients have active tuberculosis (22.7 per cent). In 20 of these 32 unsuccessful cases active tuberculosis is present on the operated side, in 12, in the contralateral lung. Of the 20 late failures with active disease beneath

TABLE 4  
*Postoperative Complications*

Wound infections	25 (11.9 per cent)
Postoperative spreads	
Contralateral	6
Ipsilateral	13
Total	19 (11.3 per cent)
Miscellaneous	
Pleural tears	8
Cerebral vasculature	2
Pleural effusions	3
Severe hemoptysis	1
Horner's syndrome	1
Wrist drop	1

TABLE 5  
*Analysis of Fatalities*

Postoperative deaths	
Resp. insufficiency	4
Pulmonary embolism	2
Shock	1
Sepsis	1
Suicide	1
	—
	9 (5.3 per cent)
Late deaths	
Progressive disease	7
Resp. insufficiency	2
Cocaine reaction	1
Undetermined	1
	—
	11 (8.3 per cent)

the thoracoplasty, 15 had had early unsatisfactory results and persistently "positive" sputum. Active disease recurred in only 5 patients on the operated side. It should be noted that in most instances of reactivation of the disease in the untreated lung, nearly all had roentgenographic evidence of disease in that lung at the time of operation. There were 11 (8.3 per cent) late deaths (table 5). The fate of the early surgical failures and successes is shown in tables 7 and 8.

TABLE 6  
*Present Status of Patients*

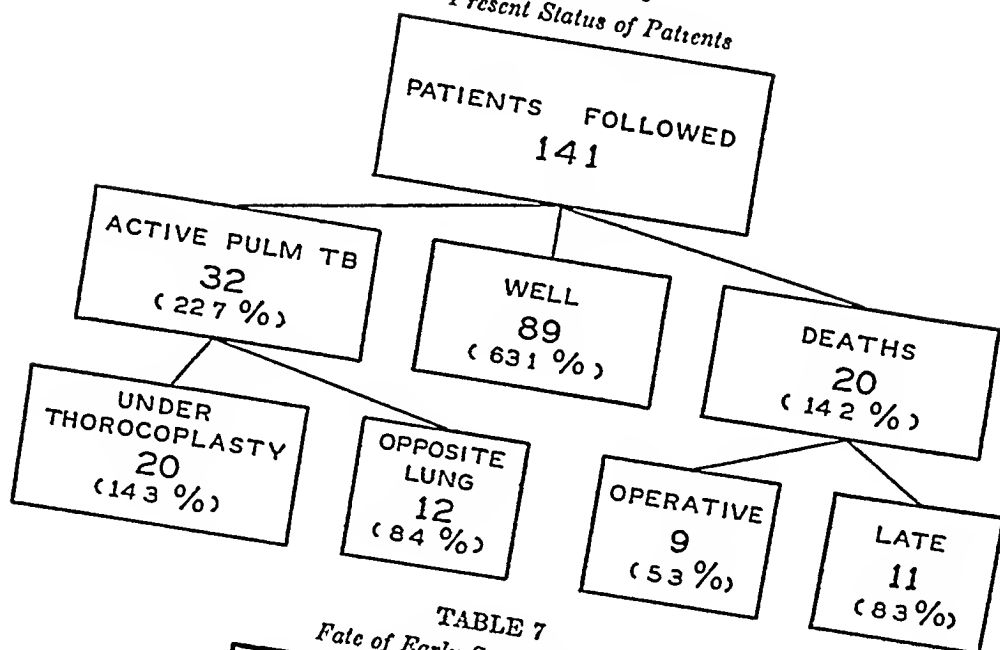
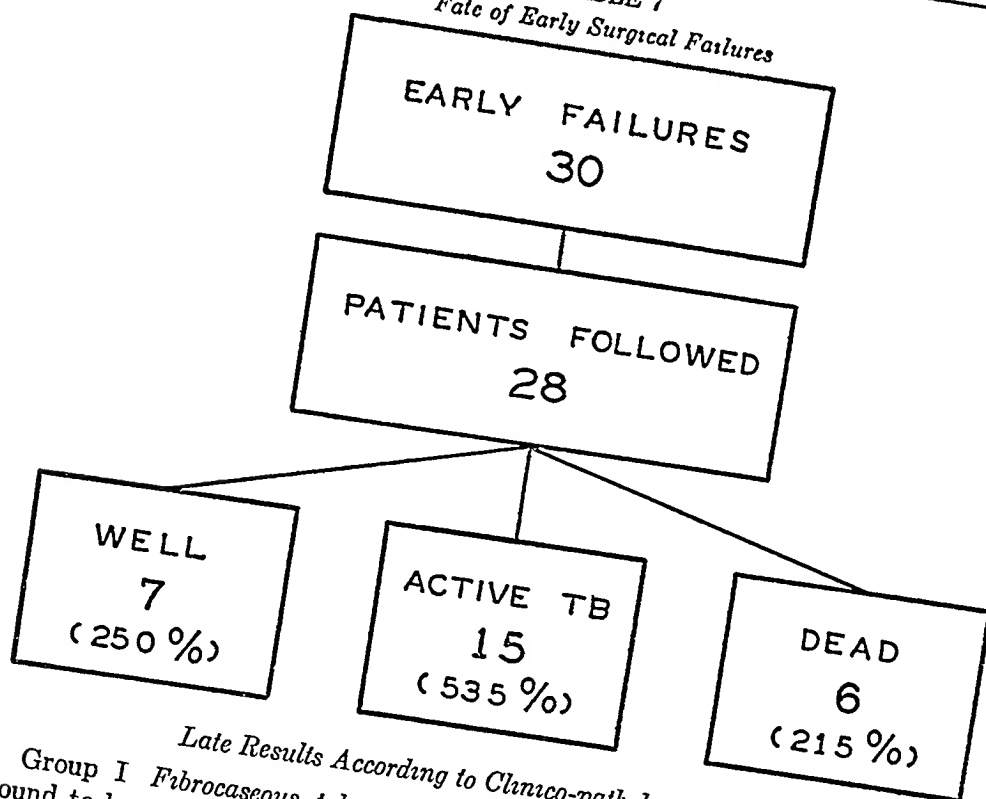


TABLE 7  
*Fate of Early Surgical Failures*

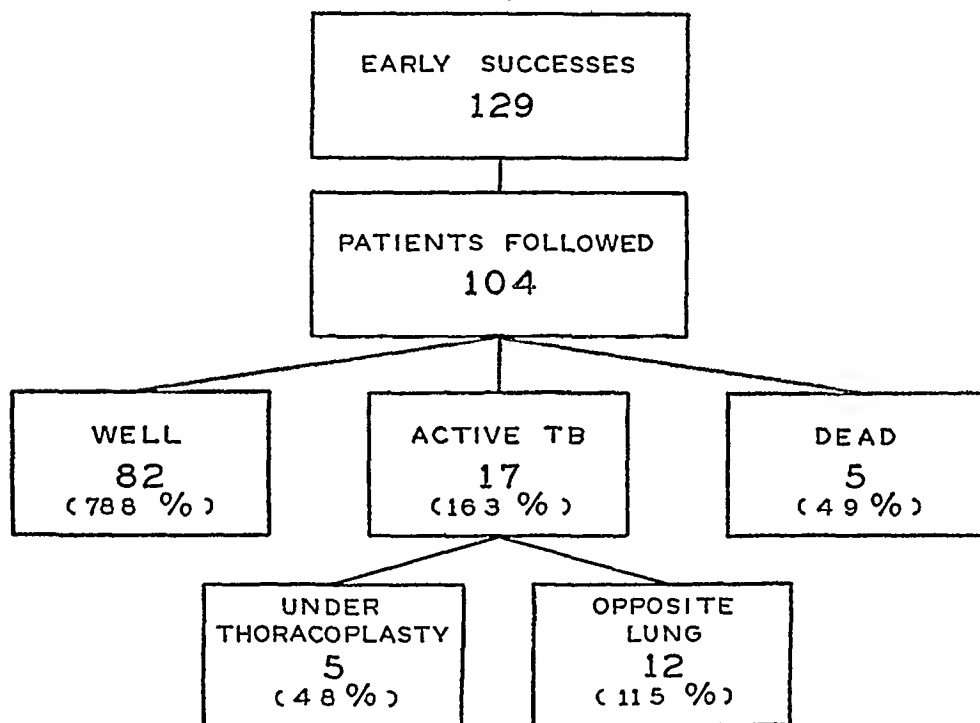


*Late Results According to Clinico-pathologic Groups*

Group I *Fibrocaceous tuberculosis* One hundred seventeen patients were found to have tuberculosis in which fibrosis predominated Active disease was

usually limited to the upper portion of the lungs and showed little tendency to progress. Cavities, varying from 2 to 4 cm in diameter, were demonstrable in almost every instance. Ninety-seven patients of this group were submitted to thoracoplasty for active disease in one lung. In 37 of these, the disease was unilateral, in 60, there were some arrested foci in the other lung. In 20 patients, there was bilateral active tuberculosis requiring bilateral collapse measures, the results of which will be analyzed separately. The immediate and late results in the 97 patients with unilateral, or predominantly unilateral, active disease are shown in table 9.

TABLE 8  
*Fate of Early Successes*

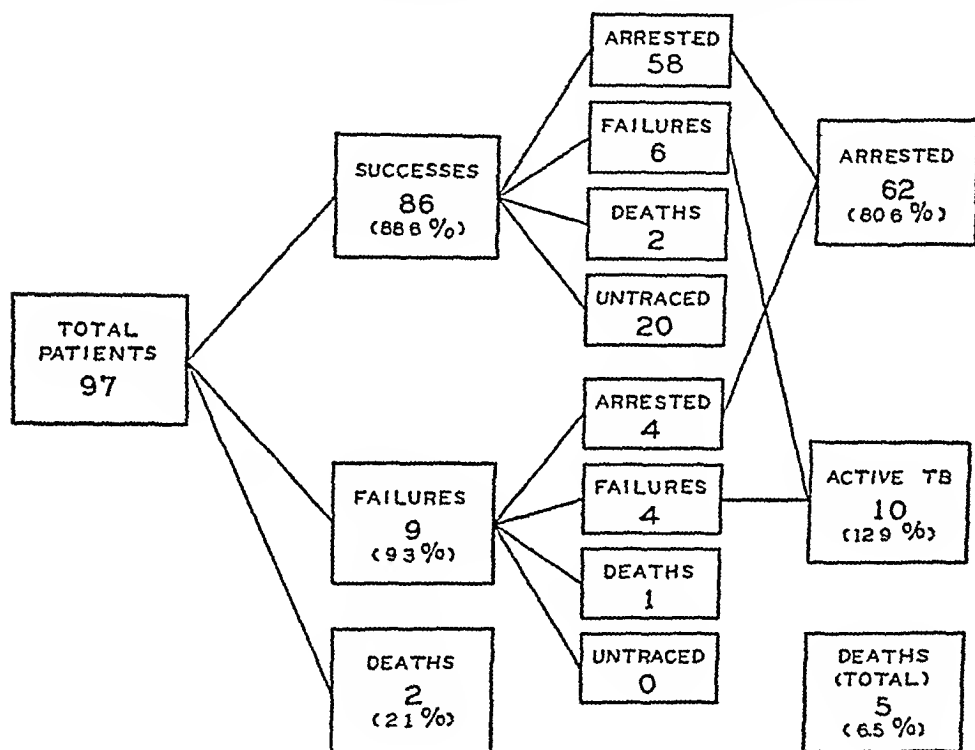


Early cavity closure and sputum "conversion" were attained by 86 patients (88.6 per cent). There were 9 early failures and 2 postoperative deaths. Seven of the 9 early failures were associated with delays in the completion of the operation as a result of wound infection in 6 and postoperative spread of disease in one. One of the deaths resulted from severe paradoxical respiration following the first stage, the other was due to pulmonary embolism, proved at autopsy, following an appendectomy performed two weeks after the first stage. The factor of interruptions will be discussed later.

The late results in 77 patients with unilateral active fibrocaseous tuberculosis reveal that 62 (80.6 per cent) are well and their disease is arrested. Of 10 patients with progressive tuberculosis, 5 have active lesions in the lung of the operated side and 5 have active lesions in the opposite lung. Four of the 5 patients with

active disease on the operated side were originally classified as early surgical failures. Four of the remaining 9 patients classified as early failures are well at present and one has died. In only one instance did a breakdown occur in the collapsed lung after a period of apparent arrest of the disease. All of the patients who developed active tuberculosis in the noncollapsed lung had evidence of inactive disease in that lung at the time of operation. There were 3 late deaths. Tuberculous meningitis accounted for one and another died suddenly from a

TABLE 9  
*Results Unilateral Active Fibrocascous Tuberculosis, Group I*



cocaine reaction preparatory to bronchoscopy. The cause of death in the third patient could not be ascertained.

Of the 20 patients with bilateral upper lobe fibrocascous tuberculosis, not included in table 9, 13 were submitted to thoracoplasty in the presence of a contralateral pneumothorax. Sputum "conversion" and cavity closure occurred in 8 patients. There were 3 early failures. One patient developed a depressive psychosis, which precluded the completion of the thoracoplasty. Active disease persisted in 2 patients. There were 2 early deaths. One patient committed suicide and the other died from respiratory embarrassment following the first stage. At the present time only 2 patients are well. Five have active disease, 4 in the re-expanded lung and one under the thoracoplasty. There were 2 late deaths,

one of which was due to progressive disease, the other to a spontaneous tension pneumothorax. Two patients could not be traced.

Seven patients were submitted to bilateral thoracoplasty. There was one postoperative death following the initial stage of the contralateral thoracoplasty due to severe paradoxical respiration. Four patients with completed bilateral thoracoplasties had arrested disease. Two, however, were followed less than two years because of very long intervals between operations and were not classified with the arrested cases (table 11). There were no late deaths. Two patients could not be traced.

The patients with active fibrocaceous tuberculosis limited to one side responded very well to thoracoplasty. The majority were between twenty and forty years of age, were good surgical risks, and had adequate respiratory reserve. Patients with bilateral thoracoplasties did better than those with contralateral pneumothoraces. Late exacerbations in the re-expanded lung accounted for many of the failures.

**Group II *Fibroid tuberculosis*** This form of tuberculosis represents the late phase of the disease described in the previous group. It is characterized by marked fibrosis and distortion of the affected lobes. Pulmonary emphysema of varying degree and dislocation of mediastinal structures are frequent sequelae. The problem presented in this group is the closure of one or more rigid-walled cavities in individuals with impaired pulmonary function. Of the 13 patients in this group, 10 were over forty years of age, 3 were in their mid thirties.

Thoracoplasty was completed in only 6 of the 13 patients, with resulting cavity closure and sputum "conversion," one of whom had considerable dyspnea following the operation. Unsuccessful results were obtained in 5 patients, in 4 of whom dyspnea prevented the completion of the operation. A residual cavity and "positive" sputum were present in the fifth patient. There were 2 postoperative deaths. Massive pulmonary embolism proved at autopsy occurred in one patient and respiratory embarrassment after the first stage was fatal in another. Dyspnea was a frequent complication in this group, occurring in 6 of the 13 patients. At present, 5 patients can be considered well and 4 are alive with active disease. One late death occurred in one of the patients with an incomplete thoracoplasty as a result of increasing respiratory embarrassment. One patient could not be traced. As in the previous group, there were no deaths as a result of progressive tuberculosis. We have recently been considering pulmonary resection in selected patients with this form of tuberculosis.

**Group III *Caseocavernous tuberculosis*** Patients with caseocavernous tuberculosis are not suitable for thoracoplasty as a rule. Nevertheless, there were 5 patients with this form of disease who had improved sufficiently to warrant an attempt at thoracoplasty with the full realization of the risks involved. The operative course was stormy in all but one. At present, 2 patients have "negative" sputum but have dyspnea on exertion which, however, does not prevent them from working. The disease progressed in the remaining 3 patients, terminating fatally in one. It is possible that streptomycin may alter the prognosis in this group.

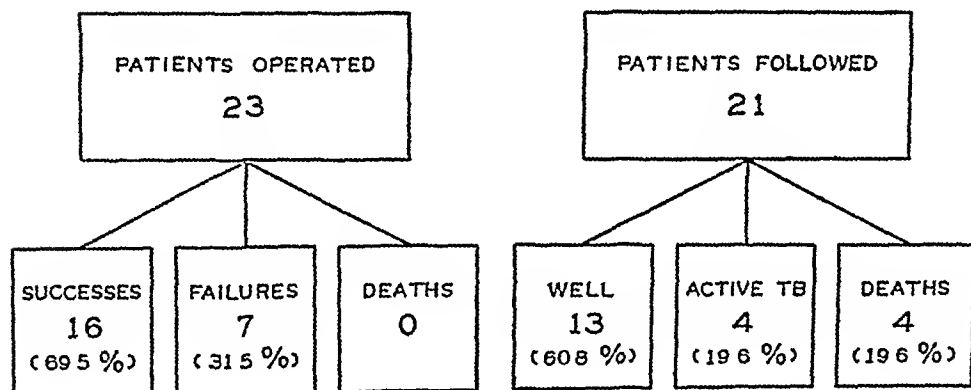
**Group IV *Tuberculosis associated with giant thin-walled cavitation*** A giant



cavity was the prominent feature of the disease in 23 patients. The cavity measured five or more centimeters in its greatest diameter, was thin-walled, and usually surrounded by disseminated disease. Large cavities due to massive caseation necrosis, which should be classified as caseocavernous tuberculosis, were not included in this group. Patients with such cavities seldom come to thoracoplasty because of the acute course of the disease. There were no instances of bilateral giant cavities. Of 17 patients bronchoscoped preoperatively, only 5 had visible endobronchial disease. One patient had laryngeal tuberculosis, the remaining 4, disease of the bronchus of the involved lobe. A study of resected specimens has revealed tuberculosis of the small bronchi in this type of lesion.

Intracavitary pressure readings performed in a number of instances disclosed the cavities to be of a tension type, a few had free bronchial communication. In

TABLE 10  
*Results Thin-walled Cavities, Group IV*  
EARLY RESULTS LATE RESULTS



several others periodic changes were noted in the bronchocavitary dynamics. In 17 patients, there was roentgenographic evidence of inactive disease in the contralateral lung. Monaldi suction was employed prior to thoracoplasty in 2 cases with diminution in the size of the cavity. Unfortunately, surgery could not be completed in either instance because of respiratory embarrassment following the first stage. One patient had amyloidosis but underwent the operation under local anaesthesia with satisfactory results. She died three years later following the development of another giant cavity of the same pattern in the contralateral lung.

Cavity closure and sputum "conversion" were achieved in 16 of the 23 patients (69.5 per cent). Seven patients (31.5 per cent) were left with residual cavities and sputum positive for tubercle bacilli. The thoracoplasty could not be completed in 4 patients because of insufficient respiratory reserve in 3 and severe asthmatic seizures in one. There were no postoperative deaths. Twenty-one of the

23 patients have been followed and 13 (60.8 per cent) are well. There were 4 late deaths (19.6 per cent), 2 resulting from contralateral disease with giant cavitation. Two of the 4 patients who were persistently dyspneic after the operation died subsequently. Four patients still have residual cavities and sputum positive for tubercle bacilli.

The difficulties encountered in obliterating giant cavities, especially those of the valvular variety, are shown by the amount of surgery required. There were more stages and more ribs resected in this group than in any of the other groups. Nine of the 19 patients, in whom the thoracoplasty was completed, underwent four or five operations and required resection of from 8 to 11 ribs to achieve cavity closure. Eleven of the 19 patients required supplementary stages and revisions.

TABLE 11  
*Late Results According to Groups*

TYPE OF DISEASE	CASES FOLLOWED	ARRESTED TB	ACTIVE TB	DEATHS
I Fibrocaceous				
Unilateral	77	62 (80.6%)	10 (12.9%)	5 (6.5%)
Bilateral	16	4 (25.0%)	7 (43.8%)	5 (31.2%)
II Fibroid	12	5 (41.7%)	4 (33.3%)	3 (25.0%)
III Caseocavernous	5	2 (40.0%)	2 (40.0%)	1 (20.0%)
IV Giant Cavity	21	13 (60.8%)	4 (19.6%)	4 (19.6%)
V Tuberculosis and Bronchiectasis	6	0 (0%)	4 (66.6%)	2 (33.4%)
VI Unexpandable lung	4	3 (75.0%)	1 (25.0%)	0 (0%)
Total	141	89 (63.1%)	32 (22.7%)	20 (14.2%)

Group V *Tuberculosis and bronchiectasis*. In 6 patients a combination of tuberculosis and bronchiectasis resulted in destruction of a lung. Symptoms referable to suppuration usually overshadowed those of active tuberculosis. Excessive cough and copious expectoration of purulent, occasionally foul-smelling sputum were particularly troublesome. Roentgenograms of the chest revealed a shrunken, destroyed lung with tuberculous cavities in the upper lobe and bronchiectasis in the remaining lobes. Four of the 6 patients had contralateral disease which was considered to be inactive at the time of operation. Thoracoplasty was unsatisfactory in every case. The operative course was stormy, in most instances because of retention of secretions which caused death in 2 patients. In a third individual, reactivation of disease in the opposite lung precluded completion of the operation. All 3 of the patients in whom thoracoplasty was completed are troubled with cough and purulent expectoration, although in one the sputum is negative for tubercle bacilli. None of the living can be considered well.

Group VI *Unexpandable lung*. Bronchoscopic examination revealed stenosis of a main bronchus in 4 patients, all of whom had unexpandable lungs. They all had had pneumothorax treatment. In this series, none were found to have an unexpandable lung secondary to a pleural membrane, in view of the fact that

patients with pleural complications were not included. Attempts at re-expansion of the lung prior to thoracoplasty in one patient resulted in a marked shift of the mediastinum to the affected side. The operation was done in this instance to reduce the amount of tracheal deviation. In the remainder, thoracoplasty was done to obliterate "dead" pleural space. All had quiescent disease at the time of thoracoplasty. There were no postoperative deaths in this group. Three of the patients are alive and well. Contralateral disease developed in one patient three years later. She had roentgenographic evidence of disease in that lung prior to the operation.

### *Effects of Operative Interruptions on the Results*

Considerable emphasis has been placed on the importance of the degree of pulmonary collapse obtained in determining the results of thoracoplasty. Failures are customarily ascribed to ineffective collapse resulting either from interruptions in the operative schedule or from an improperly performed thoracoplasty. Inasmuch as interruptions in the proper spacing of operative stages are considered particularly serious, an analysis was made of the cases in which, for one reason or another, long intervals occurred between thoracoplasty stages. Again, attention was given to the type of pulmonary lesion involved.

Interruptions in the completion of the thoracoplasty occurred in 58 patients, in most instances as a result of wound infection or spread of the disease. Of this number, 26 had an unsatisfactory result, accounting for all but 4 of the 30 early failures. Of particular significance is the fact that 19 of the 26 failures were in Groups II to V inclusive, while only 7 were in Group I, although this group was larger than the others combined (table 2). Successful results were noted in 32 patients who had had similar interruptions. Twenty-eight of the 32 cases belonged to Group I, while only 4 belonged to Groups II to V, inclusive. In Group I (fibrocaceous tuberculosis) the disease was limited and showed a natural tendency to heal. This group was found most suitable for thoracoplasty. Interruptions in the completion of the operation were not particularly serious on the final results. However, in the remaining groups which did not respond as favorably to thoracoplasty because of rigid or tension cavities, bronchiectasis, or cavities in the paramediastinal area, delays in the staging of the operation were particularly detrimental. The type of lesion present in these groups required as complete a surgical collapse as possible to achieve a satisfactory result, which was frequently impaired by the delay between stages.

### DISCUSSION

A study of the results of thoracoplasty in the various forms of pulmonary tuberculosis indicates that the nature of the tuberculous process has considerable bearing on the final outcome of the operation. Although the majority of the cases (Group I, fibrocaceous) present a type of disease which responds satisfactorily to thoracoplasty, there are a number of smaller groups in which the operation is not nearly as effective and which account for almost all the surgical failures. The poor results obtained with caseocavernous tuberculosis are obviously

a consequence of the rapidly progressive nature of the disease. There are groups in which the disease appears sufficiently stabilized to warrant surgery, but other factors inherent in the basic pathologic pattern, such as rigid cavity wall, unpredictable thin-walled cavity, tuberculosis bronchitis, associated suppurative bronchiectasis, or the presence of a markedly thickened pleura, militate against a successful thoracoplasty.

The best results with thoracoplasty are obtained in the group of unilateral active fibrocascous tuberculosis. It is quite apparent that the ultimate statistical picture of the operation in a large series of cases depends considerably upon the size of this group. Unless the results of thoracoplasty are analyzed according to the types of disease treated, the significance of this important factor is not appreciated. In the present series the operative and late mortality rates were lower for the fibrocascous group than for the entire series. Likewise, there were few late recurrences (tables 2, 6, and 9).

Thoracoplasty for fibroid tuberculosis is associated with a large percentage of failures. These result not only from the difficulty in effectively collapsing markedly fibrotic lesions associated with emphysema but also because of the impaired respiratory function which may accompany this type of disease. The majority of the patients with fibroid tuberculosis are over forty years of age and have been ill for many years. In the present series the operation was complicated by dyspnea and residual disease in almost 50 per cent of the patients in this group. Unusual care must therefore be exercised in selecting patients with fibroid tuberculosis for thoracoplasty.

The results of thoracoplasty in the group of large, thin-walled cavities are unpredictable. The disease became arrested in approximately 60 per cent of our patients, many of whom required extensive surgery to achieve this result. The difficulties encountered in the closure of such cavities result in great part from the presence of check-valve mechanisms in the draining bronchi. Recently, in such cases we have employed thoracoplasty from below upward with the intention of anchoring the lung below the cavity so that the latter is prevented from dropping into the thoracic cage. In a comparable number of cases, this procedure has eliminated the need for additional or supplementary operations. Of late, pulmonary resection is also being used with increasing frequency in the treatment of these patients with large, thin-walled cavities.

The treatment of fibroid tuberculosis and bronchiectasis with thoracoplasty is very disappointing. Because of the associated bronchiectasis, the operation is often complicated by retention of secretions and bronchogenic dissemination of the disease. Although sputum "conversion" occurred in some of the patients, the survivors continue to be plagued by symptoms referable to the mixed infection. Recent experience indicates that resection followed by thoracoplasty is preferable, especially in view of the added protection offered by streptomycin.

#### SUMMARY

An analysis has been made of the results obtained in 168 patients with pulmonary tuberculosis who were treated with extrapleural thoracoplasty. The purpose

of the study was to evaluate the factor of the type of disease under treatment in relation to the late results of the operation. None of the patients received streptomycin.

The late results for the entire series were as follows. Of 141 patients traced who had had thoracoplasty from two to six years previously, 63.1 per cent had arrested tuberculosis and 22.7 per cent active disease. The operative mortality was 5.3 per cent and the over-all mortality 14.2 per cent. All but 5 of the 168 cases had stabilized lesions at the time of surgery. Operative complications resulting in delays in the completion of the thoracoplasty were analyzed. It was found that the outcome of such delays depended to a great extent on the type of lesion.

The entire series of cases was then classified according to the type of lesion and the results of the operation compared for each group. The largest group consisted of patients with unilateral fibrocaceous tuberculosis. The best results of thoracoplasty were obtained in this group. Only one patient with an initially successful result had a "breakdown" under the thoracoplasty. It is the size of this group which determines the over-all statistical results of thoracoplasty.

Giant thin-walled cavities, thick-walled cavities, and tuberculosis with bronchiectasis accounted for most of the failures in the series. It was not the size of the cavity *per se* but the underlying pathologic pattern which influenced its closure with thoracoplasty. Currently, these types of cases are being treated preferably with resection in combination with streptomycin. It will take a number of years before it will be possible to assess the results of such treatment.

#### SUMARIO

##### *Influjo de la Forma de la Enfermedad sobre el Resultado de la Toracoplastia en la Tuberculosis Pulmonar*

Este análisis comprende 168 tuberculosos pulmonares tratados con la toracoplastia extrapleurar, teniendo por objeto justipreciar la relación que guardaba la forma de enfermedad con los resultados tardíos de la operación. Ninguno de los enfermos recibió estreptomicina.

Los resultados tardíos para toda la serie fueron éstos. De 141 enfermos descubiertos que habían sido objeto de una toracoplastia de dos a seis años antes, 63.1 por ciento tenían tuberculosis estacionada y 22.7 por ciento activa. La mortalidad operatoria fué de 5.3 por ciento y la global de 14.2 por ciento. Todos los casos, menos 5, tenían lesiones estabilizadas en la fecha de la operación. Analizadas las complicaciones quirúrgicas que hicieron demorar la terminación de la toracoplastia, observóse que el resultado de tal demora dependía en gran parte de la forma de la lesión.

Toda la serie fué clasificada después conforme a la forma de la lesión, comparándose el resultado de la intervención en cada grupo. El grupo más numeroso constaba de enfermos con tuberculosis fibrocacea unilateral, y en este grupo fué que la toracoplastia obtuvo sus mejores resultados. Un solo enfermo con resultado inicial bueno experimentó una "recaída" con la toracoplastia. La

magnitud de este grupo es lo que determina el resultado estadístico global de la toracoplastia

Las cavernas gigantes de paredes delgadas, las cavernas de paredes gruesas y la tuberculosis con bronquiectasia comprenden la mayor parte de los fracasos de la serie. No el tamaño *per se*, sino el subyacente patron patológico de la caverna fué lo que afectó el cierre de la misma con la toracoplastia. Actualmente, esos casos son tratados de preferencia con la resección combinada con la estreptomycin, mas tardarán varios años antes de que sea posible valorar el resultado de ese tratamiento

# PLEURAL DECORTICATION IN PULMONARY TUBERCULOSIS<sup>1 2 3</sup>

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## INTRODUCTION

The problem of tuberculous empyema and its precursor, the unexpandable lung following pneumothorax, has long been a disturbing one. Woodruff (1) in a review of 135 cases found that 28 per cent of the pure tuberculous empyemas and 60 per cent of the patients with mixed infection died within five years. In more than half of the fatalities the disease was minimal in the opposite lung, indicating that the tuberculous pleuritis was an important, if not the principal, factor in causing death. Of those surviving more than five years, over half remained under treatment.

Stimulated by the excellent results obtained with decortication in hemothorax during World War II (2, 3), a number of surgeons have extended the procedure to tuberculous empyema in its established and incipient forms (4, 5, 6, 7, 8, 9, 10). There are now enough cases reported to indicate that the procedure may be successfully applied in tuberculosis as far as obliterating the abnormal pleural space and re-expanding the lung are concerned. In the few years that have elapsed since adoption of the procedure, it appears that two of the feared complications, dissemination of the tuberculous process and development of tuberculous sinuses in the surgical wounds, are infrequent occurrences. This is largely credited to the use of streptomycin during the surgical period.

## OBSERVATIONS

### *Indications for Decortication*

We consider three classes of cases to be suitable for decortication: the frank empyema, the persistent abnormal space with thickened membrane and without suppuration, and the abnormal space which tends to become obliterated by extreme shifting of the mediastinum and overexpansion of the opposite lung.

Obliteration of the abnormal space and re-expansion of the lung is most easily accomplished in the nonsuppurative cases in which decortication is performed as soon as it is determined that satisfactory re-expansion of the lung cannot be accomplished by nonsurgical means. Satisfactory expansion by nonsurgical means implies that the lung will expand progressively to fill the space without extreme shifting of the mediastinum or overinflation of the opposite lung.

<sup>1</sup> From the Departments of Thoracic Surgery and Thoracic Medicine, Birmingham Veterans Administration Hospital, Van Nuys, California.

<sup>2</sup> Presented before the Medical Section, as part of the symposium on *Surgery*, at the 45th annual meeting of the National Tuberculosis Association, Detroit, Michigan, May 5, 1949.

<sup>3</sup> Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

Decortication is relatively difficult in the frank tuberculous empyemas of either the mixed or unmixed type, sharp dissection being required for much of the separation. Complete re-expansion of the lung is not always obtained, and all of our surgical complications have occurred in this group. This has made us appreciate the importance of anticipating established frank empyemas and performing decortication before extreme fibrosis occurs.

The degree of activity of the tuberculosis in the underlying lung plays an important part in deciding whether or not decortication should be performed. If acute tuberculous pneumonitis is present, one should wait until the process has subsided before considering decortication. In those cases in which there is extensive fibrosis, one may wish to obliterate the empyema, even though re-expansion of the lung following decortication is improbable. In these cases, we have followed decortication with thoracoplasty. The thoracoplasty need not be of the conventional type with removal of transverse processes and the first rib, since its only purpose is to obliterate the space left by the incompletely expanded lung.

TABLE 1  
*Precursor of Pleural Membrane*

Induced pneumothorax	8 cases
Spontaneous effusion	1 case
Induced followed by spontaneous pneumothorax	1 case
Pneumothorax and pneumonolysis	5 cases

If the thoracoplasty is for the purpose of compressing a pulmonary lesion, however, it is performed according to accepted procedure.

If bronchoscopy reveals a fibrous stenosis of a major bronchus or if broncho-pleural fistulae are present which probably cannot be closed satisfactorily, the involved lung or segment of lung should be resected at the time of decortication.

It is preferred that the patient have had no previous courses of streptomycin treatment which would cause the microorganisms to be drug-resistant at the time of operation. Experience with streptomycin in decortication and in other surgical procedures indicates that local activation of the disease and spread to other parts of the lungs is apt to occur if streptomycin is not used or if streptomycin has been given previously.

### *Etiology*

Pneumothorax, either induced or spontaneous, was the precursor of the tuberculous pleuritis in all but one of our cases (table 1). The exception was a case of spontaneous empyema classified as tuberculous by history, but not proved. In 5 of the 15 patients, pneumonolysis had been performed subsequent to pneumothorax and the sequence of events indicates that the complication of fixed abnormal space with thickened membrane and pleural effusion was a result of the pneumonolysis.

### *Pathology*

In the very earliest stage of development of the pleural membrane there is an opacification of the pleura without gross evidence of a membrane. Microscopic



examination of the pleura at this stage shows a thin fibrino-fibrous membrane moderately infiltrated with leukocytes and histiocytes and richly vascularized. This is a reversible phase in which re-expansion can probably be obtained by nonsurgical means. (Observation based on specimen obtained from a pneumothorax case at the time of lobectomy.)

The next stage of progression is represented by a grossly recognizable membrane with the visceral portion 2 or 3 mm. in thickness and the parietal portion



FIG. 1 G. L. (Case 12) Nonsuppurating membranous sac removed to obliterate abdominal space and permit re-expansion of lung.

varying from 3 to 7 or 8 mm. in thickness (figure 1). The membrane has a hyalinized fibrous middle layer and markedly vascular attached and peripheral layers. Typical tuberculous lesions are usually evident in all of the layers. The fluid in the pleural space is clear or moderately turbid, and may be positive for *M. tuberculosis*. The pleural endothelial layer may still be recognized. In this stage the process may be considered irreversible if nonsurgical means fail to produce re-expansion of the lung after a trial of several months.

The frank empyema presents a greatly thickened and roughened pleural membrane with purulent fluid within the sac (figures 2 and 3). Usually all vestiges of the endothelial layer are lost, and the fibrotic process extends into the substance

of the pleura and even into the lung. The middle hyalinized layer may show any or all stages of inflammation and degeneration, from areas of localized acute abscesses to areas of calcification. Tuberculous lesions may be present with or without excision. The ribs show degenerative changes and tend to assume a triangular form in cross section.



FIG. 2 R. P. (Case 9) Moderately severe tuberculous empyema. Note "roughened" lining in contrast to smooth lining in figure 1. Thickened peripheral ring marks the junction of the visceral and parietal portions of the membrane.

In addition to the alterations of the pleura, the underlying lung may be folded into bizarre patterns, with areas of atelectasis presumably resulting from the distortion induced by the constricting membrane. These findings are emphasized because it is thought by some that the restriction of the lung induced by the membrane is a favorable situation even though the abnormal pleural space is undesirable. In several of our cases large segments of folded lung have been observed, with atelectasis distal to the resultant bronchial obstruction.

#### RESULTS

Fifteen operations of decortication have been performed on patients in whom active tuberculosis of the lung had been diagnosed at some period during the

illness and in whom a thickened membrane had existed for periods ranging from several months to more than twenty years. At present eighteen months have elapsed since the first operation and four months since the latest operation. There have been no deaths and the abnormal space has been obliterated in all



FIG 3 A R (Case 15) Old empyema sac of more than 20 years' duration. Note shaggy lining. Sharp dissection required for most of its separation from the lung.

TABLE 2

*Unsuccessful Therapy for Obliteration of Space before Decortication*

Abandonment of pneumothorax with or without aspiration	9 cases
Streptomycin intrapleurally (0.2 Gm. 3 times weekly over 86 day period)	1 case
Thoracoplasty (resulted in draining sinus)	1 case
Phrenic paralysis	3 cases

except one of the cases. The single failure is in a patient who had been previously treated with streptomycin. In two instances, thoracoplasty was added to complete the obliteration of the space. These were cases of frank empyema.

Obliteration of the abnormal pleural space had been attempted in all of the cases prior to performing the decortication (table 2). Nine of the 15 patients had been treated by abandonment of the pneumothorax with or without aspiration

of fluid. One patient was treated with aspirations followed by intrapleural injections of 0.2 Gm. of streptomycin three times a week for eighty-six days. A thoracoplasty with the removal of a major portion of eleven ribs not only failed to obliterate the empyema in one of this series, but resulted in a draining tuberculous sinus which did not heal until the empyema sac was removed by decortication (case 8).

Five of the cases in the series were classified as frank tuberculous empyemas and 3 were classified as empyemas complicating pulmonary tuberculosis with no histologic or bacteriologic evidence of active tuberculous infection at the time of decortication (table 3). The empyemas have been eradicated in all except the patient who had received a previous course of streptomycin therapy. In 2 of the cases, stationary active disease was present in the contralateral lung at the time of decortication. In neither case has any evidence appeared of spread of the pulmonary tuberculosis following surgery. In 2 of the empyema cases, thoracoplasty was performed to complete the obliteration of the space (table 4). This was done at the time of decortication in one case, and three weeks after decortication in the other. In one patient, phrenic paralysis was performed one week

TABLE 3  
*Types of Cases Decorticated*

Unexpanded lung with clear fluid	7 cases
Undrained empyema	7 cases
Draining empyema	1 case

11 of the membranes showed histologic evidence of tuberculosis

after decortication to obliterate a small persistent space. Thoracoplasty was performed to compress underlying pulmonary lesions in 2 cases. In one instance, thoracoplasty has been advised to compress a pulmonary lesion but has not yet been accepted by the patient.

Seven cases were classified as unexpanded lung without evidence of suppuration. All of these had been treated by medical means for at least three months in an attempt to obliterate the space. In one instance the decortication was performed to arrest extreme mediastinal shift and overexpansion of the contralateral lung. Eradication of the space with complete re-expansion of the lung has been obtained in all of these cases without the addition of other surgical procedures.

Measurements of pulmonary function before and after decortication have been made by indirect methods which reflect the degree of altered function. Vital capacity, breath-holding time, and inspiratory and expiratory films indicate that an appreciable increase in function has been obtained. In general, the total pulmonary function is decreased in the first month but is increased over the pre-operative level after three months (table 5).

#### *Surgical Procedure*

The preparation for surgery and the operative technique used in these cases has been previously discussed by us (6, 7) and only a brief description will be given here. Strepto-



FIG 4 F S (Case 8) This series illustrates a case in which thoracoplasty not only failed to obliterate the tuberculous empyema, but resulted in a tuberculous sinus of the thoracic wall. Subsequent decortication under streptomycin coverage obliterated the empyema and eradicated the sinus.

a (Upper) Before thoracoplasty

b (Lower left) After thoracoplasty and before decortication

c (Lower right) After decortication

mycin, 10 Gm daily intramuscularly, is started five to seven days before operation, and penicillin, 200,000 units daily intramuscularly, is started three days before operation. At

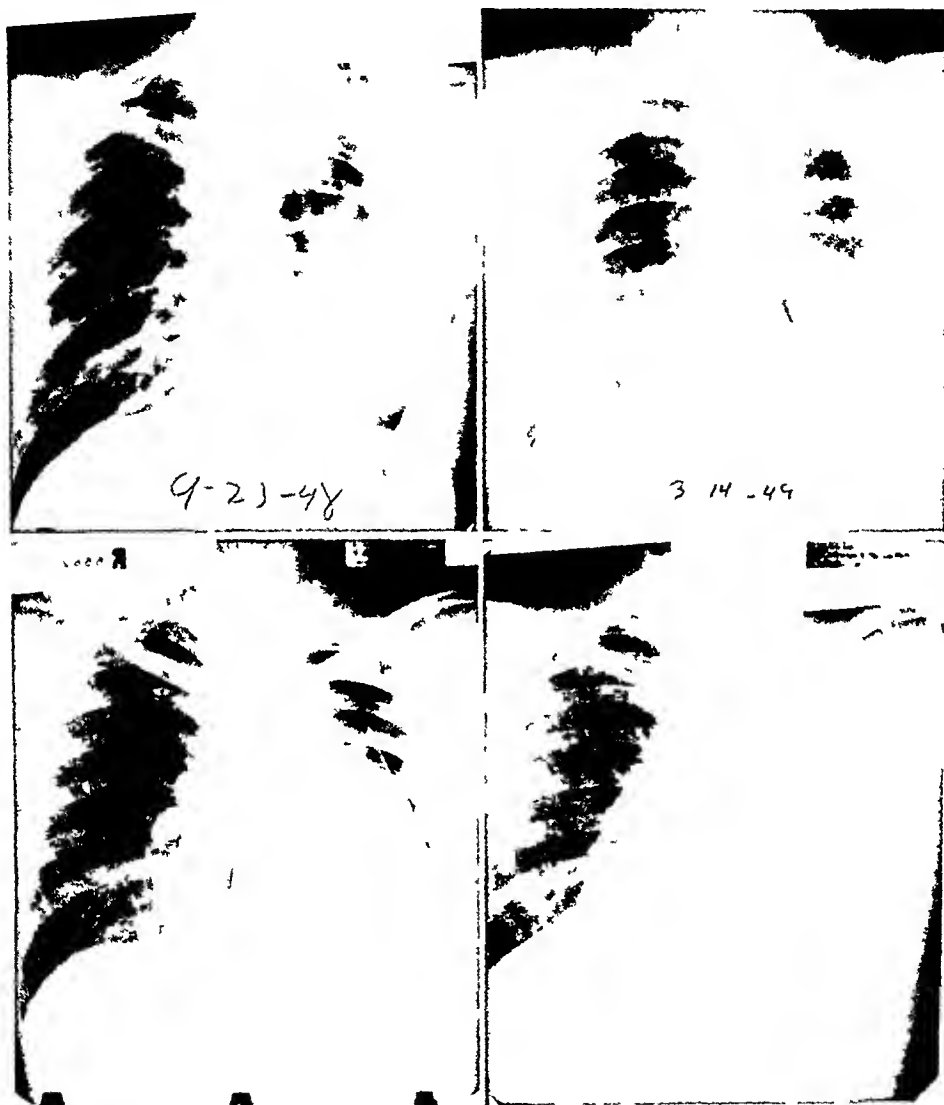


FIG 5 W T (Case 13)

- a (Upper left) Tuberculous empyema before decortication
- b (Upper right) Nine weeks after decortication. Lung has expanded and empyema has been obliterated without deformity of thoracic wall

FIG 6 I S (Case 11)

- a (Lower left) Before decortication
- b (Lower right) Four weeks after decortication. Thoracoplasty performed three weeks after decortication to compress a left apical pulmonary lesion

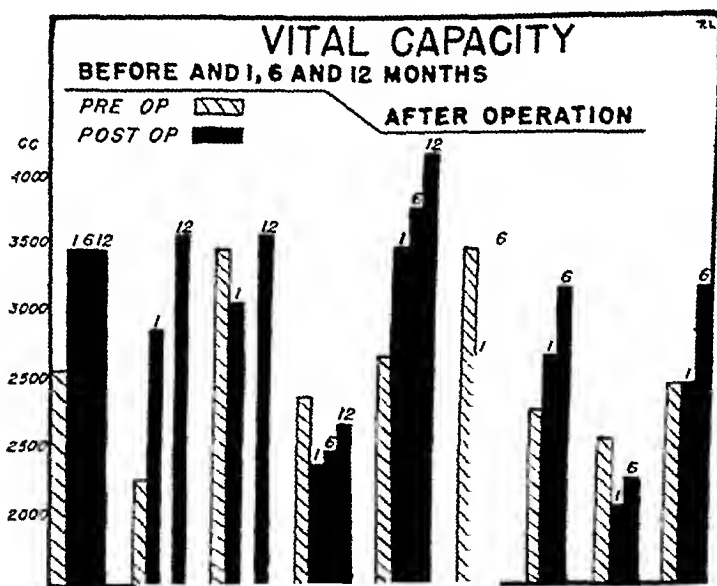
the present time a closed system of ether anesthesia is used with an endotracheal catheter. The patient is placed in a near supine position with the affected side slightly elevated to

permit extension of the thoracic incision to the posterior axillary line. An intercostal incision is made, preferably in the fifth interspace, and exposure is obtained by means of a Finochietto rib spreader. No ribs are removed or divided. The membrane is separated from the costal wall and visceral surfaces, and also from the diaphragmatic surface if a cleavage plane is readily developed. The membrane is preferably removed in one piece as this facilitates the maintenance of the cleavage plane and thus minimizes trauma to the lung. Drainage

TABLE 4  
*Additional Surgery following Decortication*

Thoracoplasty	
To complete obliteration of abnormal space	2 cases
To compress underlying pulmonary lesions	2 cases
Phrenic paralysis	
To complete obliteration of abnormal space	1 case

TABLE 5



catheters are inserted anteriorly and posterolaterally through separate stab wounds before closing the surgical incision, and these are later connected with a mild suction apparatus. The tubes are removed within several days following operation.

### *Surgical Complications*

In one instance several hundred cubic centimeters of fluid containing *M. tuberculosis* were evacuated spontaneously through the surgical wound one month after decortication. This patient had received a course of streptomycin therapy prior to consideration of decortication, and it is probable that his organisms were resistant to streptomycin at the time of surgery. The sinus, which formed at the site of evacuation of the fluid, became closed in six weeks. Thoracoplasty has been advised to complete the obliteration of the persistent pleural space, but

has not yet been accepted. The patient is classified as a failure at the time of the preparation of this report, but it is too early to predict the final result. It is significant that this was the only case in which a course of streptomycin therapy had been given some time prior to surgery.

The only serious surgical complication was in a patient whose empyema had existed for more than twenty years. In this case a portion of the diaphragm was removed with the membrane, due to obscuration of the field by excessive bleeding. He now has a moderate herniation of the stomach into the thorax, but his recovery has been uneventful otherwise. He has no symptoms referable to the herniation. This experience has made us realize the danger of decorticating the diaphragm in long standing cases of frank empyema, and we would advise against the removal of this portion of the membrane if separation cannot be obtained easily by blunt dissection.

There have been three instances of fracture of a rib due to pressure of the retractor blades. In none of these instances did the patient complain of intercostal pain following surgery.

One case with postoperative leakage of air from the pulmonary surface required reopening of the surgical wound nine days after decortication because of failure of the lung to expand. At reoperation the leak was sealed with "fibrin foam" held in place with fine cotton sutures. Following this the patient made a very satisfactory recovery with complete obliteration of the pleural space. This case was described in an earlier report (6).

#### CASE REPORTS

The first 7 of the 15 cases comprising this study have been reported in earlier articles (6, 7).

*Case 8* F. S., male, age 25, was diagnosed pulmonary tuberculosis, far advanced, left, in January 1946. Pneumothorax, left, was started at that time and was discontinued in March 1946. Turbid green fluid was aspirated on several occasions between July 12 and August 16, 1946.

On admission to Birmingham Veterans Administration Hospital he showed a left hydro-pneumothorax, with adhesions between the apex of the lung and the thoracic wall and with several cavities in the left upper lobe. The fluid was positive for *M. tuberculosis*. An eleven-rib thoracoplasty was performed in four stages between August and November, 1946. The patient left the hospital in February 1947 against medical advice. He returned in September 1947 because of a draining sinus in the lower part of the thoracic wall which communicated with a tuberculous pleural empyema. Bronchoscopy at this time showed no evidence of bronchial obstruction. Decortication was decided on, and the patient was prepared for surgery. The preoperative preparation included the administration of streptomycin, 1.0 Gm. daily intramuscularly, beginning October 31, 1947.

Operation was performed on November 13, 1947. A lateral thoracic incision was made over the tenth rib and a portion of necrotic rib was removed. The pleural empyema space, which extended from the diaphragm upward for 8 cm., was resected except for a small area near the apex. A catheter drain was placed through a separate stab wound and was connected with a suction apparatus. One Gm. of streptomycin and 200,000 units of penicillin were dissolved in distilled water and instilled into the pleural space. The thoracic wall incision was closed in layers with interrupted cotton sutures.



The surgical wound healed primarily. Penicillin therapy was discontinued four days after operation and streptomycin therapy was discontinued sixty days after operation. Phrenic nerve crush was performed November 21, nine days after operation, because of a questionable pleural space. Planigrams made subsequently showed complete obliteration of the space. *M. tuberculosis* could not be demonstrated in the fluid at the time of operation, but microscopic examination of sections of the membrane showed typical tubercles with caseation and epithelioid cells. The patient left the hospital against medical advice three and one-half months after decortication. At that time the sputum was "converted" and there was no evidence of residual empyema. Indirect reports indicate that his course has been favorable up to the present time (figure 4).

**Comment.** This patient is an example of chronic tuberculous empyema in which extensive thoracoplasty failed to obliterate the space and resulted in a draining sinus through the thoracic wall.

In the light of experience, the phrenic paralysis which was induced nine days after operation was probably unnecessary and we do not recommend it as a routine procedure following decortication.

**Case 9.** R. P., male, age 26, was diagnosed as having pulmonary tuberculosis in August 1947. The disease was unilateral with cavitation in the left apex. Pneumothorax was started November 21, 1947 and apical pneumonolysis was performed in February 1948. Fluid, which developed following severance of adhesions, was positive for *M. tuberculosis*. The pneumothorax was abandoned August 4, 1948 because of persistent fluid and formation of a pleural membrane. His last sputum culture positive for *M. tuberculosis* was obtained on March 29, 1948. Roentgenographic examination on July 9, 1948 showed a cavity in the left apical region, mediastinal shift to the left, narrowing of the interspaces, thickening of the pleura, and fluid in the pleural space.

Decortication was performed August 13, 1948 after one week of streptomycin, 1.0 Gm daily intramuscularly. The parietal membrane, 0.5 to 1.0 cm in thickness, was separated by finger and gauze dissection. The visceral membrane, 0.3 cm in thickness, was separated by blunt and sharp dissection except for a small adherent patch which was left on the lingula. The membranous sac had a capacity of approximately 700 cc and presented a granular inner surface (figure 2). It showed typical tubercles histologically. Drainage tubes were inserted in the usual manner.

His postoperative course was uneventful. The tubes were removed on the fourth day. The lung has remained fully expanded since then. Streptomycin was continued for a full forty-two day course because at the time of surgery nodes which were possibly the site of active tuberculosis were palpated in the lung.

The vital capacity, which was 2,300 cc before operation, was 2,700 cc one month after operation and 3,200 cc six months later.

**Case 10.** W. L., male, age 48, was diagnosed as having pulmonary tuberculosis in 1926. A right pneumothorax was started that year and was continued for seven and one-half years. A pleural effusion which developed was aspirated at various times in the following years. His last sputum positive for *M. tuberculosis* was obtained in 1938.

Shortly after his admission to this hospital, 175 cc of turbid purulent fluid were aspirated from the right pleural space. At this time his chief symptoms were weakness and fatigue. There was no evidence of active pulmonary tuberculosis. Roentgenographic examination showed opacification limited to the lateral half of the right thorax.

Streptomycin, 1.0 Gm daily intramuscularly, was started one week before decortication. At surgery the ribs were overlapped, thickened, and markedly degenerated. Two ribs were fractured by the rib spreader in exposing the pleura. The membrane was separated by blunt and sharp dissection from the parietal and visceral surfaces, not including the diaphragm.

matic surface. The membrane measured up to 2.0 cm in thickness in some areas. Very little expansion of the lung was obtained and portions of four ribs were resected to complete the obliteration of the space. Postoperative recovery was uneventful. The space remains obliterated several months after operation.

Cultures and histologic examination of the membrane were negative for tuberculosis. It was markedly hyalinized throughout and was calcified in many areas. The vital capacity which was 2,100 cc before operation had dropped to 1,600 cc one month after operation. The breath-holding time remained constant. Further determinations of function have not yet been made.

*Comment.* This empyema is representative of the type which may persist for years with only mild general symptoms but which is a continuing source of systemic infection. At the time the patient was seen by us, thoracoplasty would not have obliterated the hard-shelled space and a Schede operation would have been the only alternative surgical procedure.

*Case 11.* J. S., male, age 25, was first found to have pulmonary tuberculosis in June 1945. A left pneumothorax was induced in July 1945 because of an apical cavity. Pneumonolysis, performed October 10, 1945, resulted in a persistent pleural fluid accumulation. Temporary phrenic paralysis was induced November 5, 1946. The pneumothorax was abandoned July 6, 1948 because of thickening of the pleura which probably had its inception in December 1945. Bronchoscopy at this time showed no evidence of bronchial occlusion.

A left pleural decortication was performed August 25, 1948 after the usual preparation, including streptomycin intramuscularly. A thick-walled empyema sac of 700 cc capacity and containing fibrino-purulent material was removed, mostly by gauze and finger dissection. Some sharp dissection was required over the pulmonary surface and several pulmonary air leaks were sealed with "fibrin foam." The distal half of the lingula was amputated because of a large soft caseated abscess in its tip.

The postoperative course was without complications. A left four-rib thoracoplasty was performed three weeks later to compress an apical lesion (figure 6).

The vital capacity and breath-holding time, which were 3,200 cc and 32 seconds, respectively, before operation, were 2,300 cc and 28 seconds one month after operation. Later determinations have not yet been made.

A full forty-two day course of streptomycin was given to this patient.

*Case 12.* G. E., male, age 26, was found to have left subapical tuberculosis in December 1945. Left pneumothorax was started in April 1946 and continued for two years.

At the time of admission to Birmingham Veterans Administration Hospital there was thickening of the pleura with fixation of the lung, fluid, mediastinal shifting to the affected side, and narrowing of the intercostal spaces. Bronchoscopy showed evidence of tracheal shift.

Decortication was performed September 10, following the usual preliminary examination and preparation. Separation of the total membrane was accomplished without difficulty. The membranous sac had a capacity of about 800 cc (figure 1). A caseous area was uncovered just below the apex. Its contents were evacuated and the space filled with "fibrin foam" to seal an air leak.

The postoperative course was without untoward incident. Streptomycin was continued to complete a forty-two day course of 1.0 Gm daily intramuscularly.

The vital capacity and breath-holding time, which were 2,800 cc and 30 seconds before operation, were 3,500 cc and 55 seconds six months after operation.

*Case 13.* W. T., male, age 28, was found to have far advanced pulmonary tuberculosis on the left in April 1947. Pneumothorax was started in May 1947. Fluid formed in April 1948.

and aspirations of fluid were performed at intervals of a few months. The pneumothorax was abandoned in September 1918 because of increasing fluid. He entered this hospital a few weeks later with evidence of thickened pleural membrane, fixed lung, and shift of the mediastinum to the affected side. A moderate hydropneumothorax was present. Bronchoscopy was negative except for evidence of a shift of the trachea to the left.

A left decortication was performed January 5, 1919 after one week of streptomycin therapy. Separation of the sac in one piece was accomplished without difficulty. The sac was lined with a shaggy fibrino-purulent membrane and had a capacity of about 500 cc.

The postoperative course was without complications. Streptomycin, 10 Gm intramuscularly daily, was continued to complete a forty-two day course of treatment of the pulmonary disease.

The vital capacity and breath holding time, which were 3,500 cc and 35 seconds before surgery, measured 3,000 cc and 40 seconds one month after surgery. Subsequent measurements have not yet been made.

**Case 14.** L. B., male, age 38, was found to have far advanced, bilateral, severe pulmonary tuberculosis in October 1915. A right pneumothorax was started in January 1916 and was discontinued at the time of admission to Birmingham Veterans Administration Hospital in September 1918 because of a mixed pleural infection. At this time there was almost complete obscuration of the right lung and evidence of exudative disease in the left midlung field. The sputum was positive for *M. tuberculosis*. Bronchoscopy revealed a moderate hyperemia of the left upper lobe bronchus and a shifting of the trachea to the right.

The patient had received a forty-two day course of streptomycin treatment beginning November 22 and ending December 2, 1918. This included 10 Gm daily intramuscularly and 0.2 Gm intrapleurally three times a week. The left pulmonary lesion regressed under this therapy, but the condition of the right pleural empyema remained unchanged.

Decortication was performed January 6, 1919 after resuming streptomycin therapy one week earlier. The membrane was removed as an intact shell. Sharp dissection was required over most of the pulmonary and diaphragmatic surfaces. The empyema sac contained a greenish gray fibrino-purulent exudate. The lung was fully expanded at the time of closure of the surgical wound.

There was evidence of a pleural effusion one week after operation, but it could not be located with an aspiration needle. One month after surgery several hundred cubic centimeters of clear fluid were evacuated spontaneously through the surgical wound. The fluid was positive for *M. tuberculosis* by culture. The sinus formed by the escaping fluid became closed six weeks later. However, the space occupied by the fluid has not been obliterated. Thoracoplasty has been advised, but the patient has left the hospital to attend to personal problems not directly related to his illness. This was against the advice of his physicians.

**Comment.** This patient must be counted as a failure at the time of this report. However, if thoracoplasty is performed in the near future, obliteration of the space may yet be accomplished.

This case presents indirect evidence of the hazard of performing decortication if the patient has had a previous course of streptomycin therapy with probable resulting loss of therapeutic effect on the microorganisms.

**Case 15.** A. R., male, age 51, was first discovered to have tuberculosis in 1918. The basis for the diagnosis is not known to us. He was given bed rest therapy from 1918 to 1920. During that period he developed a left pleural effusion which was aspirated on numerous occasions for several years. He experienced moderate dyspnea and weakness in the years following, but was able to carry on regular activities.

In October 1947 the symptoms of dyspnea and weakness became pronounced. Repeated aspirations of the left pleural space showed a turbid fluid, negative for *M. tuberculosis* and other pyogenic organisms.

He was admitted to Birmingham Veterans Administration Hospital October 16, 1918. Examination revealed a fixed left lung with greatly thickened pleural membrane and turbid fluid in the left pleural space. There was an extreme narrowing of the intercostal spaces and the mediastinum was displaced to the affected side. A diagnosis of chronic empyema was made, with probable spontaneous onset some time within several years following the year 1918.

Inasmuch as the pyothorax was increasing in severity, as indicated by the increase in the severity of symptoms and the physical signs, decortication was decided upon.

Streptomycin, 10 Gm daily intramuscularly, was started January 22, 1949. Penicillin, 300,000 units daily, was started January 24.

Decortication was performed January 26. An incision was made in the left fifth interspace from the parasternal line to the posterior axillary line. Removal of the membrane from the costal surface was performed by blunt dissection, but against much greater resistance than in previous cases. Separation of the membrane from the pleural surface was almost entirely by sharp dissection. Although large areas of pulmonary parenchyma were exposed, air leakage was minimal and had practically subsided at the time of completion of the operation. In separating the membrane from the diaphragmatic surface, an area of several square centimeters of the membranous portion of the left hemidiaphragm was removed with the empyema sac. This was due to firm fibrotic adherence of the membrane to the diaphragm and to obscuration of the field by bleeding which was more than that usually encountered. Because this operation was associated with excessive trauma and bleeding and had consumed more time than previous operations, it was decided not to attempt closure of the defect in the diaphragm. Four liters of blood were given intravenously during the decortication. The lung had not fully expanded to fill the pleural space at the end of the operation, because of pulmonary fibrosis.

The patient's course was very satisfactory following surgery, notwithstanding a moderate herniation of the stomach into the pleural space. The pleural space was reduced to a pocket of several cubic centimeters at the time of preparation of this report. Postoperative determinations of the vital capacity and breath holding time have not yet been made.

*Comment.* It is assumed that this long standing chronic empyema was of tuberculous origin, probably the result of a spontaneous tuberculous pleural effusion. This case is an example of acute exacerbation of inflammation in an empyema that had been dormant for many years.

The difficulty encountered in separating the membrane from the diaphragm has made us wary of attempting to include this portion of the membrane in the decortication in cases in which there is firm fibrotic adherence between the membrane and the diaphragm.

#### SUMMARY

Fifteen patients with unexpandable lung and persistent pleural space following unsuccessful pneumothorax have been treated by total or almost total decortication of the pleural membrane. The cases include various degrees of thickened pleural membrane, from simple thickening with clear fluid accumulation to frank draining empyema.

There have been no deaths, and the few surgical complications have not interfered with eradication of the abnormal pleural space.

In 2 cases with frank empyema, the lung did not expand completely and it was necessary to add limited thoracoplasty to accomplish obliteration of the space. In 2 others, thoracoplasty was added to compress underlying pulmonary lesions. In another, the only case which may be considered a possible failure, thoraco-

plasty has been advised to complete the obliteration of a persistent space but has not yet been accepted by the patient

Indirect measurements indicate that there is an immediate postoperative decrease in total pulmonary function, with an appreciable increase in function after several months. In most of the cases, the eventual function is beyond that estimated immediately before operation.

Streptomycin, 1.0 Gm daily, was used during the surgical period, beginning several days before operation and continuing for two to five weeks after operation, depending upon the degree of pulmonary pathology. In the only case in which a course of streptomycin therapy had been given prior to decortication, a pleural effusion containing *M. tuberculosis* developed one month after decortication. This is the possible failure mentioned above.

Decortication is performed more easily and with less danger of surgical complications in those cases which have not reached the stage of frank empyema. For this reason we believe that the operation should be performed as soon as it is decided that medical treatment will not satisfactorily obliterate the abnormal pleural space.

It is now more than eighteen months since our first operations were performed. There has been no evidence of spread of pulmonary tuberculosis and there has been only one case in which tuberculosis of the pleura was possibly activated by the decortication, the case in which streptomycin therapy had been given previously with probable loss of sensitivity.

#### SUMARIO

##### *La Decorticación Pleural en la Tuberculosis Pulmonar*

A 15 enfermos con pulmones inexpandibles y persistente espacio pleural a continuación de un neumotórax fracasado, se les trató con la decorticación total o casi total de la membrana pleural. Los casos comprenden varios grados de espesamiento de la membrana pleural, variando de mero espesamiento con acumulación de líquido diáfano a franco empiema supurante.

No ha habido mortalidad, y las pocas complicaciones quirúrgicas no han vedado la erradicación del espacio pleural anómalo.

En 2 casos con empiema declarado, el pulmón no se expandió completamente y fué necesario agregar una toracoplastia limitada para conseguir la obliteración del espacio. En otros 2, se agregó la toracoplastia para comprimir lesiones pulmonares subyacentes. En otro caso, el único que puede considerarse como posible fracaso, se ha aconsejado la toracoplastia para completar la obliteración de un espacio persistente, pero el enfermo no la ha aceptado.

Mediciones indirectas indican que se presenta una disminución postoperatoria inmediata de la función pulmonar total, con aumento apreciable al cabo de varios meses. En la mayor parte de los casos, la función definitiva es superior a la estimada antes de la operación.

Durante el período quirúrgico, se empleó estreptomicina, 1.0 gm diario, comenzando varios días antes de la intervención y continuando hasta dos a cinco semanas después, de acuerdo con la patología pulmonar presente. En el único

caso en que se había dado una serie de estreptomycinoterapia antes de la decorticación, se presentó un derrame pleural que contenía *M tuberculosis*, un mes después de la decorticación. Este es el posible fracaso mencionado más arriba.

La decorticación se ejecuta con mayor facilidad y menos peligro de complicaciones quirúrgicas en los casos que no han llegado a la etapa de empiema declarado, por cuya razón debe realizarse apenas se decida que el tratamiento médico no obliterará a satisfacción el espacio pleural anormal.

Han transcurrido más de dieciocho meses desde que se verificaron las primeras operaciones. No ha habido signos de difusión de la tuberculosis pulmonar y sólo existe un caso en el que la tuberculosis pleural fué posiblemente activada por la decorticación, aquél en se había administrado antes estreptomicina con probable pérdida de la sensibilidad.

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#### *Discussion of Paper by Doctors Weinberg and Davis*

*Dr Victor H Kaunitz, Mt Morris, N. Y.* I should like briefly to present two cases which illustrate some of the points made by Doctor Weinberg. Artificial pneumothorax is designed as a temporary collapse procedure but, unfortunately, at times, it becomes permanent because of the thickened fibrous membrane formed over the lung, parietal pleura, and diaphragm. In performing a decortication, the surgeon is attempting to carry out the plan the medical man had at the start of treatment, namely, to return the collapsed lung to as near normal function as possible. Although, as has been mentioned, the amount of function restored depends to a large extent upon the amount of disease previously present in the lung, it would seem that greater function would be regained if both the diaphragmatic and parietal surfaces were decorticated, as well as the visceral pleural surface.

The first case is that of a 30 year old white male whose tuberculosis was discovered while in the service, in April 1945. A left pneumothorax was begun in May 1945, for cavity in the superior segment, left lower lobe. A left pneumonolysis was performed in July 1945. Fluid in varying amounts was present in the left pleural cavity and was always negative for acid-fast bacilli. Sputum was converted, and the pneumothorax was maintained for three and

a half years. Re-expansion was attempted late in 1948, but was unsuccessful. The patient was dyspneic on moderate physical activity. The left chest was motionless on deep inspiration, as was the left diaphragm. A left decortication was done March 10, 1949, with removal of the complete fibrous envelope in one piece. The postoperative course was uncomplicated, and four weeks after operation there is motion of the left chest wall and diaphragm. This operation was not difficult technically and total blood loss, measured by the weighed sponge technique, was 600 cc.

In cases with considerable active tuberculosis still present in the collapsed lung, or with stenosis of the main or lobar bronchi, decortication may be combined with resection and thoracoplasty. This combination of procedures is also applicable to tuberculous empyema.

The second case was that of a 32 year old white female who was admitted to the hospital in 1937 with left lower lobe cavity. Left temporary phrenic, repeated twice, was ineffective in producing cavity closure, and pneumothorax was started in May 1939. Ulceration of the left main bronchus was observed in 1941. This progressed to partial stenosis. Pneumothorax was maintained, and sputum was intermittently positive for tubercle bacilli. Tuberculous empyema developed in 1945, with fluid remaining positive, and with the lung about 50 per cent collapsed, despite repeated aspirations and attempts to re-expand it. Because of the partial stenosis and the positive sputum, excision of the empyema sac combined with pneumonectomy was decided on as the procedure of choice. This was done on February 1, 1949. Thoracoplasty through the eighth rib was done seven weeks later, to partially obliterate the left pleural cavity. The wounds healed by primary union, and postoperative courses were uncomplicated.

# TUBERCULOSIS IN NURSES CLINICAL OBSERVATIONS ON ITS PATHOGENESIS AS SEEN IN A FIFTEEN YEAR FOLLOW-UP OF 745 NURSES<sup>1 2, 3</sup>

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## INTRODUCTION

During the past twenty years various concepts about the course and prognosis of tuberculosis in nurses have been presented. This study presents the clinical aspects of the pathogenesis of tuberculosis as a first or primary infection in nurses, whether it occurred in those who entered training as reactors or nonreactors to tuberculin. The report concludes a series of observations by one of the writers (1, 2, 3) on a group of nurses who entered training during the period February 1932 to February 1943, inclusive.

## PLAN OF STUDY

There is nothing new in the execution of this study except the long duration of the follow-up observations. The general procedure was similar to that used in investigations in this country by Amberson and Riggins (4), Shipman and Davis (5), Geer (6), and Myers (7), and to the studies in Norway by Heimbeck (8).

All nurses were examined clinically and roentgenographically and were tested with Saranac Old Tuberculin on entrance to training. None with tuberculous lesions were admitted to training. Tuberculin tests and roentgenographic examinations of the lungs were carried out at six month intervals, although a number of nurses were unable to follow the routine because of affiliations in other hospitals or the interference of night duty.

All nurses were originally admitted as regular students to training school at the Boston City Hospital for a three year course. There has been no tuberculosis section in the hospital itself during the entire period of this study and cases of tuberculosis were scattered throughout the medical wards. Usually all tuberculous patients were segregated on the porches, but in some wards this was not possible. In 1937 one of the writers (T. L. B. (1)) recorded that there were approximately 12,300 hospital days of open pulmonary tuberculosis a year per thousand hospital beds, while patients awaited transfer to sanatoriums. In the last year of this

<sup>1</sup> From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

<sup>2</sup> Presented in part before the Medical Section, as part of the symposium on *Research and Therapy*, at the 44th annual meeting of the National Tuberculosis Association, New York, New York, June 17, 1948.

<sup>3</sup> This study was made possible through a grant from the Committee on Medical Research and Therapy of the American Trudeau Society, medical section of the National Tuberculosis Association.



study there were approximately 12,000 hospital days of pulmonary tuberculosis in the hospital. All nurses, however, had one month of student training at the Sanatorium Division of Tuberculosis for the City of Boston. No *strict* "contagious technique" was established in either the hospital or the sanatorium. The nurses were instructed in the necessity of frequent hand washing as a most essential precaution, in addition to the thin mask and gown that was worn.

#### *Nature of follow-up*

The follow-up study was carried out on a group of nurses whom the war had scattered and marriage had taken to distant parts of the country. Questionnaires, which were the initial contact, were answered in full by 612 of the 732 nurses still living, or 83.5 per cent. Roentgenographic examinations of the lungs were obtained and reviewed on 300 of the total group, or 40 per cent.

Detailed information, in addition to the questionnaires, was obtained concerning health and occupation through families, classmates, private physicians, Army, Navy, Veterans Administration, and the Public Health Service. This applied especially to those who were uncooperative, and sufficiently accurate information was obtained to make us believe that almost every case of tuberculosis was unearthed. Therefore the over-all figures are based upon the entire group of 745 nurses.

There were 71 cases of tuberculosis. Detailed information is lacking concerning one individual whose death from tuberculosis was officially reported. The roentgenograms of two cases were not obtainable for review but descriptions of the lesions were available as to location and size.

It is the purpose of this study to present the clinical data of a long term follow-up of tuberculosis. Discussion of the subjects of so-called "primary" and "reinfection" disease in young adults will center primarily around the clinical course, treatment, and prognosis of the 71 cases of tuberculosis which developed following admission to training until the close of the observation period. No nurse is included in the study with an observation period of less than five or more than fifteen years.

### OBSERVATIONS

#### *Incidence of Tuberculosis*

It is of interest in the first place that the tuberculin negative and positive reactors were almost equally divided on admission (table 1).

Secondly, while somewhat more tuberculosis appeared in the initial non-reactors over the fifteen years, there was no statistically significant difference in the total amount of disease appearing in the two groups (table 2).

Fifty-two, or 14 per cent, of the non-reactors remained negative throughout training. Therefore, if the total amount of tuberculosis in the initially positive reactors is compared with the amount of disease which appeared in those who converted from "negative" to a "positive" tuberculin test, there is a noticeably higher incidence of tuberculosis in the group which "converted" (table 3).

The 71 cases of tuberculosis include one case of cervical lymphatic disease proved by biopsy, 66 cases of pulmonary tuberculosis, and 4 cases of pleurisy.

TABLE 1

*Number and Per Cent Distribution of All Nurses Studied, Classified by Result of Initial Tuberculin Test 1932-1948*

RESULT OF INITIAL TUBERCULIN TEST	ALL NURSES STUDIED	
	Number	Per cent distribution
All results	745	100 0
Reactors on entry	374	50 2
Non-reactors on entry	362	48 6
Result of initial test unknown	9	1 2

TABLE 2

*Number and Per Cent of Nurses Studied Who Developed Tuberculosis, Classified by Result of Initial Tuberculin Test 1932-1948*

RESULT OF INITIAL TUBERCULIN TEST	ALL NURSES STUDIED		
	Total	Those who developed tuberculosis	
		Number	Per cent of total
All results	745	71	9 5
Reactors on entry	374	31	8 3
Non-reactors on entry	362	40	11 0
Result of initial test unknown	9	—	—

TABLE 3

*Number and Percentage of Initial Non-reactors, among Nurses Studied Who Subsequently Developed Tuberculosis, Classified by Status of Reaction throughout the Training Period 1932-1948*

STATUS OF REACTION THROUGHOUT TRAINING PERIOD	ALL INITIAL NON REACTORS		
	Total	Those who developed tuberculosis	
		Number	Per cent of total
All groups	362	40	11 0
Converted to positive	285	38	13 6
Remained negative throughout	52	2*	3 8
Status of reaction unknown	25	—	—

\* Developed subsequent to training period after late conversion of tuberculin

with effusion without demonstrable parenchymal disease Hereinafter the mention of tuberculosis in "negative" or "initially negative" reactors implies that the "negative" tuberculin test had turned positive

Thirdly, there was a closely parallel course in the rates at which tuberculosis appeared each year after entrance into training in the two groups of tuberculin reactors, expressed in rates per 1,000 observation years (figure 1)

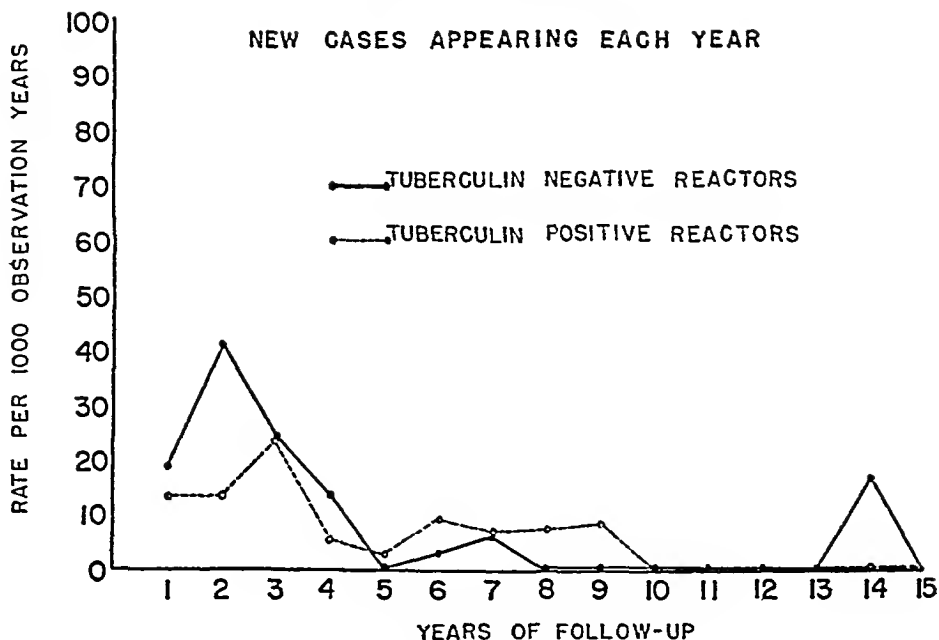


FIG 1 Case rates of tuberculosis in initially negative and positive reactors per 1,000 observation years

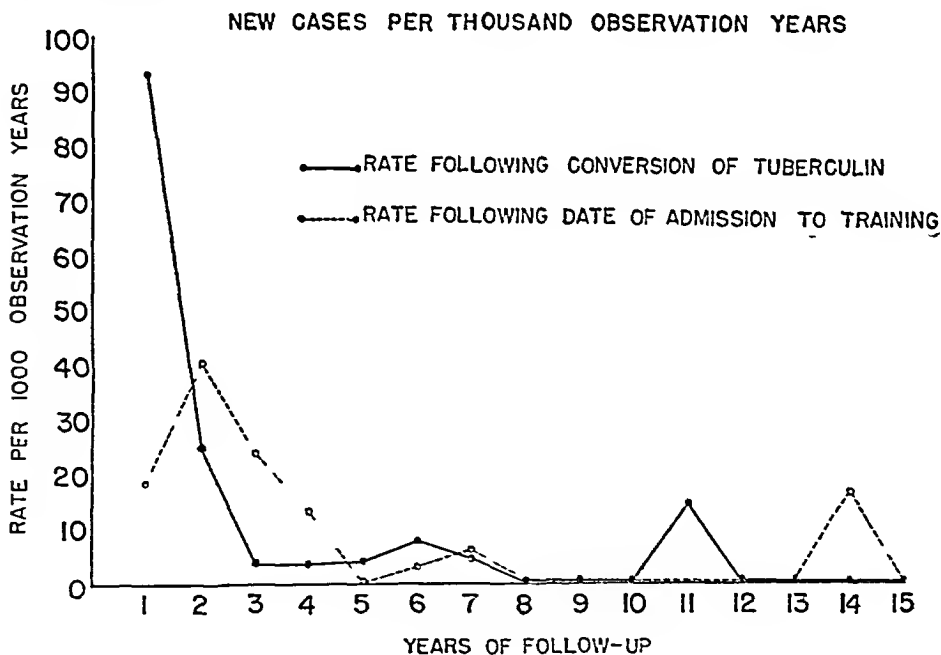


FIG 2 Case rates of tuberculosis in negative reactors each year following conversion of tuberculin compared to their appearance following admission to training

If the tuberculosis of the negative reactors on admission is analyzed, however, and its appearance in years from date of entry is compared with its appearance

in years following date of "conversion" from tuberculin negative to positive, a different picture is presented (figure 2)

In table 4 may be seen the number and per cent of new cases occurring each year and during each five year period. The appearance of new cases in both groups of reactors following admission to training, as well as appearance in time following conversion of tuberculin, are compared. In the initially negative reactors 55 per cent of the tuberculosis appeared within two years after admission to training while 32 per cent of tuberculosis in initially positive reactors appeared

TABLE 4

*New Cases among Reactors and Non-reactors upon Admission and among Non-reactors after Conversion, Classified by Year 1932-1948*

YEAR	REACTORS UPON ADMISSION		NON REACTORS UPON ADMISSION		NON REACTORS AFTER CONVERSION	
	Number	Per cent distri- bution	Number	Per cent distri- bution	Number	Per cent distri- bution
1 to 15 years	31	100 0	40	100 0	40	100 0
1 to 5 years	22	70 9	36	90 0	36	90 0
1 year	5	16 1	7	17 5	26	65 0
2 years	5	16 1	15	37 5	7	17 5
3 years	9	29 0	9	22 5	1	2 5
4 years	2	6 5	5	12 5	1	2 5
5 years	1	3 2	—	—	1	2 5
6 to 10 years	9	29 0	3	7 5	3	7 5
6 years	3	9 7	1	2 5	2	5 0
7 years	2	6 5	2	5 0	1	2 5
8 years	2	6 5	—	—	—	—
9 years	2	6 5	—	—	—	—
10 years	—	—	—	—	—	—
11 to 15 years	—	—	1	2 5	1	2 5
11 years	—	—	—	—	1	2 5
12 years	—	—	—	—	—	—
13 years	—	—	—	—	—	—
14 years	—	—	1	2 5	—	—
15 years	—	—	—	—	—	—

in the same period. These values are to be compared with the 85 per cent of disease demonstrable in the initially negative two years following the date of *conversion of tuberculin to positive*.

At the end of the first five year period there is a close approximation in the rate of appearance of tuberculosis in all three groups.

#### *Deaths from Tuberculosis*

The 4 who died of tuberculosis were divided between "negative" and "positive" reactors. In the "negatives" both were far advanced disease when discovered. One (Case 1, appendix) developed her disease three years after completion of training, while she was a patient in a psychiatric institution. She died

four months after the initial diagnosis, with rapidly progressive bilateral tuberculosis. The other (M R Case 33, appendix) is described below. She died eighteen months after the acute pneumonic onset of her disease.

In the 2 "positives" who died, one (Case 46, appendix), is known to have died after finishing training, according to the records of the Massachusetts Department of Public Health and information from her classmates. Details of onset and course were not obtained.

The other (Case 50, appendix), developed minimal disease at the end of the first year of training. She received sanatorium care, left against advice, broke down again, was readmitted two years later, again left against advice and died of massive hemorrhage at home.

The 3 very interesting cases of disseminated lupus erythematosus have been reported elsewhere (11).

TABLE 5

*Deaths among Nurses Studied, Classified by Cause of Death 1932-1948*

CAUSE OF DEATH	TOTAL DEATHS
All deaths	13
Tuberculosis	4
Lupus erythematosus disseminata	3
Accident and suicide	2
War casualties	2
Staphylococcus septicemia	1
Carcinoma	1

### *The Character of Tuberculosis in the Tuberculin Negative and Positive Reactors*

A brief outline of all 71 cases of tuberculosis is found in the appendix, and the following case histories in more detail are samplings of only a few of the similarities and differences that existed in the tuberculosis which developed in the two groups of tuberculin reactors.

### *Case Reports*

#### *Progressive minimal disease in an initially negative reactor*

*Case 1, M H C* (Case 8, appendix). The patient was an 18 year old, very blond young nurse, who was admitted to training with a *negative* tuberculin test in September 1932. In July 1934, her tuberculin test was first positive, in association with a fever of undetermined origin which appeared along with subjective involvement of some of the smaller joints. She was hospitalized at that time (July 1934) where she remained at bed rest. A thorough search for the cause of low grade fever was made and it was finally decided that it was probably rheumatic in origin. The patient was discharged home in December 1934, after five months of bed rest, and she returned to duty in January 1935 feeling well. A week after starting work, she fainted on the ward, was hospitalized again, and was found to have fever (100° F) with some recurrence of joint pain. She was transferred to a hospital for rheumatic fever. Here she was symptom-free for a few weeks, then showed a slowly rising temperature. Three months after admission she developed cough and sputum. A roentgenogram of the

chest showed extensive infiltration of the left upper lobe and many tubercle bacilli were present in the sputum

On subsequent review of the roentgenogram, it was noted that in July 1944 a small area of infiltration, 1.0 cm. in diameter, was present in the periphery of the left third interspace. This density had not been seen during her hospital admission. Moreover, in January 1935, when she returned to work, there was a node in the region of the right hilum which was not visible on previous or subsequent films. The patient subsequently developed tuberculosis of the sacroiliac joint which necessitated confinement in a cast for eighteen months. In addition, a left artificial pneumothorax was maintained for six years. At present a small, residual, well-calcified lesion is present in the apex of the left upper lobe. The patient is living a normal life, with a full-time job.

This girl with a negative tuberculin test initially was found to be tuberculin-positive when she developed her first infection with tuberculosis. Her minimal lesion progressed to far advanced disease in spite of eight months of bed rest. Her joint symptoms, her active sacroiliac disease, and her pneumonic spread suggest a hematogenous spread of her tuberculosis.

*Progressive minimal disease in an initially positive reactor*

*Case 2, A. C. H.* (Case 56, appendix) The patient was a 19 year old girl who was tuberculin-positive and had a normal chest roentgenogram on entrance to the training school. She developed a 1.5 by 2.0 cm. lesion in the right midchest two years after admission to training. She was entirely symptom-free and no abnormal findings could be elicited on physical examination. Another roentgenogram one month later showed what was thought to be a central highlight. On re-examination four days later, however, this abnormality was no longer visible and at no time subsequently did it reappear. She remained at part-time work with extra rest. Roentgenograms of the chest were repeated at monthly intervals and the size of the lesion steadily diminished and the patient felt well.

In spite of her good progress, nineteen months after the first lesion was seen, there appeared on routine examination a new 5.5 by 2.5 lesion at the left apex. Once again it was entirely asymptomatic and without physical signs. She was hospitalized and given bed rest along with left artificial pneumothorax for eleven months. The latter was then abandoned as unsatisfactory after two pneumonolyses. No further complications occurred. Her recovery was uneventful and at present she is well, with both lesions well calcified, and is able to work full time.

This case represents reactivation of tuberculosis in a *positive* reactor. The course of events is probably very similar to the preceding case except for the long hiatus of well-being during which she remained on duty, between the appearance of the first lesion and the second one on the opposite side.

*A healing minimal lesion in an initially negative reactor while on duty*

*Case 3, M. C. S.* (Case 38, appendix) This 18 year old girl entered training in September 1935, with a *negative* tuberculin test and a negative roentgenogram of the chest. Because of a severe streptococcus pharyngitis two months after admission, she stopped training and was readmitted in the next class five months later. At this time her tuberculin test was *strongly positive* to 0.001 mg. of Old Tuberculin. Roentgenographic examination of her chest revealed a homogenous density 1 by 3 cm. in the periphery of the right first interspace. She refused treatment but was cooperative in her monthly check-up. No further sign of her lesion could be seen after five months, but in October 1947 an irregular calcified deposit was noted at the site of her early lesion. At present she is entirely well and able to manage her household, which includes one-year old twins.

This patient represents what must have been a "first infection" with tuberculosis in one whose resistance was good. Her pattern was parenchymal disease without demonstrable regional lymphatic enlargement.

*The healing of a minimal lesion in an initially tuberculin-positive Negro girl while on duty*

*Case 4, E W P* (Case 66, appendix) This 19 year old Negro girl came to training in September 1942, with a positive tuberculin test and a negative chest roentgenogram. Eleven months after admission she developed, without symptoms, a ground-glass comet-like lesion 1 by 1.5 cm. in the right third anterior interspace immediately below the interlobar septum, apparently in the right middle lobe. Because of the war and the shortage of beds in both sanatorium and hospital, she remained at work under close monthly clinical and roentgenographic examinations. By October 1946 the lesion was smaller, retracted and fibrotic, and by 1948 it apparently consisted of small calcium deposits. The patient is well and working full time now.

There is no reason to suppose that this small asymptomatic lesion was other than a first infection similar to the preceding case, which became manifest by roentgenogram within the first year of entering training. This Negro girl also showed extraordinarily good constitutional resistance. Her disease consisted of a small parenchymal lesion without demonstrable regional lymphatic enlargement.

*Acute exudative tuberculous lobar pneumonia in an initially negative reactor*

*Case 5, M R* (Case 33, appendix) This 18 year old girl, who entered training in September 1935, remained tuberculin-negative through May 1936. On September 5, 1936, she was admitted for minor urinary symptoms following a bad cold of a week's duration. She had had a "stuffy" nose and an unproductive cough, without fever.

Following admission to the hospital she rapidly developed high fever with pneumonic consolidation of the entire left upper lobe, over a ten day period. Her sputum became positive for acid-fast bacilli and her tuberculin test was positive for the first time. Transferred to a sanatorium, she was given artificial pneumothorax, did well for about a year, then developed another pneumonic spread to the right side with cavitation. She died 18 months after the onset of her disease.

This acute pneumonia lesion appearing three months after a known negative tuberculin test must once again represent a first infection with tuberculosis in an individual of high sensitivity to the tubercle bacillus and low bodily resistance.

*Acute exudative lobular pneumonia in a tuberculin positive reactor*

*Case 6, E P C* (Case 47, appendix) This 18 year old girl, admitted to training in 1938, was tuberculin-positive with a negative roentgenogram and a normal physical examination. Fifteen months after admission in December 1939, she developed a pneumonic lesion in the upper third of the right lower lobe and tubercle bacilli were present in the gastric washings. Under sanatorium bed rest, she developed a cavity. She was given pneumothorax in February 1940, but the disease spread in March 1941 to the left side. In September 1941, she left the sanatorium against advice, married, and did well at home for a year and a half, maintaining her right pneumothorax. She returned in May 1943 with active disease. A left pneumothorax was induced and the right lung was re-expanded. In February 1947, the left pneumothorax was abandoned because of an obliterative pleuritis. Sputum and gastric washings have been negative for *M. tuberculosis* by examination and culture since 1944. The patient's disease is arrested and she is living a normal life.

There would seem to be very little difference between this and the preceding case. Both were acute pneumonic lesions, varying only in the anatomical extent of lung involvement. The first, a pneumonic lesion in a girl tuberculin-negative three months before onset, the second a pneumonic lesion in one tuberculin-positive at entrance. Neither presents any clinical or roentgenographic distinctions which would classify it as a primary as opposed to a reinfection type of tuberculosis. From the clinical standpoint, the disease of both patients apparently represents the same thing, a first infection, or more simply, progressive pulmonary tuberculosis.

*Pleurisy with effusion in an initially negative reactor*

*Case 7, J. F. A.* (Case 3, appendix.) This 19 year old girl was admitted to training in February 1932. She had a negative chest roentgenogram and a *negative* tuberculin test which turned positive six months after admission. In February 1933, one year after admission, a routine chest roentgenogram revealed a small mottled infiltration one sq. cm. in size in the lower segment of the right upper lobe, associated with significant enlargement of the regional hilar lymph nodes. For two days she had had a very slight pleuritic pain in the right mid-axilla without fever, cough, or loss of weight. She was removed from training and sent home on twenty-two hours' bed rest a day, which she is said to have observed for four months. Five months after the appearance of her parenchymal lesion on the right she had a bad "head cold." Two weeks later she developed an acute febrile serofibrinous pleurisy with effusion on the right, for which she received eight months of sanatorium care. Shortly after discharge she was married against advice and had three children, without exacerbation of her tuberculosis. Today she remains well and has brought up her whole family without further reactivation of her tuberculosis.

She was the first case of pleurisy with effusion definitely shown to follow in the wake of primary parenchymal infection after conversion of the tuberculin test from negative to positive.

*Pleurisy with effusion in an initially positive reactor*

*Case 8, H. K.* (Case 59, appendix.) This 18 year old nurse was admitted to training in February 1942, with a *positive* tuberculin test. In April, two months after entering training, she had a slight pleuritic-like pain in the left lower chest, with a negative roentgenogram of the chest. In May, three months after admission, she had a similar but less severe pain in the right lower chest. In June, four months after admission, she developed a small infiltration in the left infraclavicular area followed in July by a small serous effusion of the right chest. For this she took three months of sanatorium care, until October 30th. She returned directly to duty, obviously too soon, as she developed acute pleurisy with effusion on the left, together with visible enlargement of a left hilar lymph node. She received seven more months of sanatorium care. An accidental pneumothorax accompanied a chest tap on the left. Following sanatorium treatment, her disease remained arrested until 1947, when a tuberculous salpingitis was surgically removed in June of that year. At present this patient's lesions are arrested. She is married and has no children.

### *Classification and Treatment*

The lesions which we have encountered have for the most part been small pulmonary infiltrations 1 by 2 cm. in diameter with none larger than 6 by 8 cm. in the minimal group. They are classified in table 6.

Bed rest, in both "sanatorium" care and "home" treatment, included bathroom



privileges except for the few who were cared for at the Boston City Hospital where *absolute* bed rest was imposed. For the minimal lesion, six weeks to fourteen months of bed rest was instituted for those who needed no collapse therapy. The average period of bed rest was five and one-half months in both the initially negative and positive tuberculin reactors for minimal lesions.

TABLE 6

*Cases of Tuberculosis Which Developed among Initial Tuberculin Reactors and Non-reactors Studied and Classified by Initial State of Disease 1932-1948*

STAGE OF DISEASE	CASES OF TUBERCULOSIS AMONG		TOTAL CASES OF TUBERCULOSIS AMONG NURSES STUDIED	
	Initial reactors	Initial non reactors	Number	Per cent distribution
All stages	31	40	71	100 0
Pulmonary	30	36	66	92 9
Minimal	22	32	54	76 1
Moderately advanced	7	2	9	12 7
Far advanced	—	2	2	2 8
Stage of disease unknown	1	0	1	1 4
Pleurisy with effusion	0	4	4	5 6
Tuberculous adenitis	1	—	1	1 4

TABLE 7

*Specific Treatment in 71 Nurses*

	INITIAL REACTORS, NUMBER	INITIAL NON REACTORS, NUMBER	TOTAL	
			Number	Per cent
Bed rest only	11	22	33	46 5
Bed rest plus pneumothorax	9	7	16	22 6
Bed rest plus thoracoplasty	2	0	2	2 8
O P D supervision only	6	9	15	21 1
O P D plus rest	1	0	1	1 4
O P D plus pneumothorax	1	1	2	2 8
Unknown course	1	1	2	2 8
Total	31	40	71	100 0

Four to eight months of slowly increasing exercise characterized the convalescence in the uncomplicated cases. The classification of "Out-Patient Department supervision" was a routine of regular monthly general physical, roentgenographic, and laboratory examination. This group of nurses remained on duty and, with the cooperation of the training school, was usually permitted a mid-day rest, supplements to diet, and relief from night duty as long as was requested. These girls were indeed "treated" and were watched with the utmost care.

In table 7 may be seen the specific treatment procedures used in the two groups of initially negative and positive reactors.

Table 7 is self-explanatory with the exception of the cases supervised in the Out-Patient Department (O P D). A total of 18 were carried on this regimen. Fifteen received no definitive treatment while they remained at work, except regular O P D supervision. In 3 patients the lesions reactivated. One of these showed extension of her minimal lesion two years after its discovery and was treated with pneumothorax. A second (Case 2), 19 months after satisfactory regression of her small initial lesion, developed an asymptomatic spread to the contralateral apex. The third, classified as "O P D supervision," had an unreported pleurisy and twelve months later developed an apical infiltration treated with bed rest. Another patient (Case 24, appendix) is recorded as having had a "reactivation" but in reality she had a very small asymptomatic pleural effusion associated with a very small parenchymal infiltration. She was allowed to remain on duty with careful check-up and her disease has shown no reactivation in the ten succeeding years. In view of our present regard for tuberculous effusions, this girl would not be allowed to remain on duty with this lesion today.

It should be made clear at this point that all early tuberculous lesions were considered potentially progressive. When symptoms of activity also accompanied the visible roentgenographic infiltration, however, small, there was no question of the need of bed rest treatment. A careful, scrupulously detailed history remains a great necessity in these cases. Too much emphasis is likely to be placed upon the roentgenographic appearances alone. The physical examination of the lungs with these small lesions was almost always negative, but the *general physical* examination often revealed defects which were thought to bear an untoward effect on the progress of the infection.

### *Pleurisy with Effusion*

A total of 12 individuals had pleurisy with effusion, but one patient had two episodes. Nine cases appeared in the initially negative reactors, 3 cases in the "positive" reactors. Four of those in the initially negative reactor group followed several months after the appearance of a parenchymal lesion (Cases 3, 15, 59, appendix). Four cases were associated with demonstrable pulmonary disease (Cases 24, 25, 48, 67, appendix). Four cases showed no roentgenographic evidence of parenchymal disease (Cases 12, 23, 28, 36, appendix). The thirteenth episode (Case 59, appendix), was the appearance of a pleural effusion on the side contralateral to the original effusion four months previously. In the 4 patients whose pleurisy with effusion followed the appearance of a parenchymal lesion, the interval of time between the two episodes was seven months in Case 3, thirty-four months in Case 15, four months in Case 40, and two months in Case 59.

This sequence of events of pleural effusion following a minimal parenchymal lesion with and without visible lymphatic enlargement was seen in initial reactors and non-reactors. It gives visible proof of at least one pattern which is seen in the pathogenesis of pleurisy with effusion. Spread from a parenchymal lesion to the sensitized pleura may be direct by extension from a subpleural lesion or, as seems very likely but less easily proved, by the lymphatics and the blood stream to the sensitized pleura. The course of events in Case 3, with the greatly en-

larged regional lymph nodes, suggests the hematogenous route as does Case 15 with the effusion contralateral to the parenchymal disease, and Case 59 with its bilateral effusion following the left-sided parenchymal disease. It appears in these cases that pleurisy with effusion has developed as an expression of a more generalized phase of tuberculous infection after primary localization. Strictly speaking, it is an exacerbation or reactivation of primary parenchymal infection. A true primary complex of Ranke (10), with lymphatic involvement and spread to the pleura by the blood, may occur. Since the lung is the most common site of primary infection in this country, most cases of pleurisy with effusion must follow pulmonary infection. It is logical to assume, however, that bacilli from primary intestinal disease with its extensive lymphatic involvement may be another source of bacilli blood borne to an allergic pleura.

TABLE 8  
*End Results of Minimal Tuberculosis*

MINIMAL TUBERCULOSIS (54)	INITIALLY NEGATIVE (32)		INITIALLY POSITIVE (22)		TOTAL (54)	
	Number	Per cent	Number	Per cent	Number	Per cent
<b>A End Results</b>						
Finally arrested	29	90.7	19	86.4	48	88.8
Under treatment	2	6.2	2	9.1	4	7.4
Dead	0	0.0	1	4.5	1	1.9
Unknown	1	3.1	0	0.0	1	1.9
<b>Total</b>	<b>32</b>	<b>100.0</b>	<b>22</b>	<b>100.0</b>	<b>54</b>	<b>100.0</b>
<b>B Reactivations</b>						
Infiltrates	6		7		13	
Pleural Effusions	4		3		7	
<b>Total</b>	<b>10</b>		<b>10</b>		<b>20</b>	

Thus each of the eight cases of pleurisy with effusion in this series which followed parenchymal disease, or was associated with it, is classified according to the nature of pulmonary infiltration. The pleural effusion itself is classed as a *reactivation* in each of these 8 individuals. Only the 4 cases of pleurisy with effusion *without* any visible parenchymal lesion are classed initially as pleurisy with effusion. Even though it be assumed that the primary lesion in these 4 cases was in the lung and was not detected by the roentgenographic examinations at six month intervals, or was too small to be seen, the primary infection may have been intestinal in origin.

#### *End Results of Tuberculosis*

The end results of the 71 cases of tuberculosis are shown in tables 8, 9, and 10. Arrested tuberculosis also includes cases which are apparently healed. Unexpanded pneumothorax is classed as still "under treatment." *Reactivations* in-

clude asymptomatic roentgenographically demonstrable spreads of disease as well as clinically significant "spreads" Only pleurisy with effusion without visible lung disease is classed initially as such "Reactivations" apply only to those whose lesions have been "arrested" and who developed a new lesion or pleurisy with effusion at some subsequent date

Table 8, Section A, presents the end results of initially minimal tuberculosis Eighty-nine per cent of the patients are living a normal life and their disease is arrested Of the 5 still under treatment, one is receiving pneumothorax but clinically is apparently arrested The one patient who died left the sanatorium

TABLE 9

*End Results of Moderate and Far Advanced and Extrapulmonary Tuberculosis and Pleurisy with Effusion*

	INITIALLY NEGATIVE	INITIALLY POSITIVE	TOTAL
<b>A Moderately and far advanced (11)</b>			
Finally arrested	0	6	6
Under treatment	2	1	3
Dead	2	0	2
Extrapulmonary (1) (Adenitis)	0	1	1
Initial classification unknown	(1)0	1 (dead)	1
<b>B Pleurisy with effusion (4) (no infiltration of lung)</b>			
Finally arrested	4	0	4
Reactivations	2	0	2
Dead	0	0	0
	4	0	4
<b>C Summary</b>			
Totals of Table 9	8	9	17
Totals of minimal disease (Table 8)	32	22	54
Grand total	40	31	71

against advice and her disease progressed rapidly to fatal hemorrhage Reactivations, Section B, occurred as parenchymal disease in 13 patients In one individual the reactivation was an incidental finding on roentgenographic examination, was arrested at the time, and was not associated with a history of symptoms Of 13 patients with parenchymal reactivations, 3 are still under treatment, one died of hemorrhage, and 9, or 68 per cent, have arrested lesions at present

Seven cases of pleurisy with effusion in this group are classed as reactivations because they followed or were associated with pulmonary lesions One was a pleurisy on the side opposite the pulmonary infiltration and one was a bilateral effusion followed five years later by tuberculous salpingitis which was successfully treated surgically

Table 9, Section A, presents the end results of moderately and far advanced disease and extrapulmonary disease. Section B presents pleurisy with effusion without lung infiltrates. The number of cases is presented rather than percentages as the totals are small. Section C summarizes the totals in numerical figures only.

Table 10 summarizes the total reactivations of the series. Two reactivations would not have been known except for a review of roentgenograms made in retrospect. The lesions in both of the patients are now arrested. Of the 16 patients with reactivations, 4 are under treatment, one is dead, and 11 have arrested lesions and are married or working and living a normal life.

Thus these three tables, 8, 9, and 10, again show the similarity of distribution of disease and end results as seen in the initially negative and positive reactors.

TABLE 10  
*Total Reactivation in 71 Cases of Tuberculosis\**

	INITIALLY NEGATIVE	INITIALLY POSITIVE	TOTAL	PER CENT
Parenchymal Infiltrate	7	9	16	22.5
Symptomatic			14	19.7
Asymptomatic			2	2.8
Pleural Effusion	1	4	5	7.0
Total	11	13	24	33.7

\* Initial Case Distribution

66 Cases of pulmonary tuberculosis

1 Case of pleurisy with effusion

1 Case of tuberculous adenitis

#### *Tuberculosis Case Rates<sup>4</sup>*

This relatively small group of nurses had a total of 71 cases of tuberculosis, but the group was followed for five to fifteen years. Thus the over-all 71 cases of tuberculosis with 7,492 observation years from 1932 to 1948 give an attack rate of 95 per hundred per year. Fifty-six of these 71 lesions required treatment and present a rate of 74 per 100 nurses per year.

The 15 very small lesions were those O.P.D. supervised cases which might well have never been recognized but for regular six month roentgenographic examinations which revealed their presence and their uneventful regression. There is little doubt that the roentgenographic visualization of the lesion alone is deceptive as it may have little or no clinical significance. Very careful and frequent observation is necessary to establish the character of these small lesions.

Forty-five new treated lesions occurred *during training* in the 745 nurses with a case rate of 2.0 per hundred per year. Eleven treated cases occurred in the nurses *after graduation*, with a rate of 0.20 cases per hundred per year. Each group is based on its respective total observation years.

<sup>4</sup> Statistical data and rates were reviewed by Miss Jane Worcester, Assistant Professor of Bio statistics, Harvard School of Public Health.

These figures are computed on the basis of those 745 nurses who comprise the follow-up study

A total of 1,203 nurses, however, was admitted to the Training School, of whom 458 resigned for failure in studies or nontuberculous illness. These totaled 493 additional observation years. Fifty-six nurses who developed new tuberculous lesions requiring treatment were dropped statistically from observation at the time their disease developed. These totaled 356 observation years. Thus the corrected total observation years for all nurses admitted to training, minus those removed from training or observation for all causes, is 7,629. The overall rate for all 71 lesions is 93 per 100 nurses per year. For the 56 nurses needing specific treatment the rate is 73 per hundred per year.

#### DISCUSSION

*The incidence of tuberculosis in initially "negative" and "positive" reactors to tuberculin.* This horizontal study of tuberculosis in nurses reemphasizes certain concepts concerning the pathogenesis of the disease which formed the basis of an earlier report on this same group of nurses by one of the writers (T. L. B.) (2). At that time there appeared to be few or no clinical and roentgenographic features to distinguish the tuberculosis which developed, whether it occurred in reactors or non-reactors to tuberculin on admission to training. Clinically the same type of tuberculosis was observed in both groups of individuals. The factor that seemed most important in determining the pattern of disease and the course in infection was the individual's inherent constitutional resistance to tuberculosis or her lack of it. This longer fifteen year follow-up report substantiates those earlier observations and helps to clarify our own wavering conceptions of the pathogenesis of this disease.

The close parallelism of incidence of tuberculosis in "negative" and "positive" reactors in our nurses does not seem remarkable, although at variance with some other reports. It is to be expected that different results will be obtained in different hospitals, and among different age groups, and in other countries. Racial as well as individual and environment factors will influence the findings.

Shipman and Davis (5) found that most of their nurses who developed clinical tuberculosis during training were tuberculin-positive on entrance. Pollack and Cohen (12) also found a closely similar rate of tuberculosis in both negative and positive reactors, as did Israel and Long (13). On the other hand, Geer (6), Heimbeck (14, 15), Amberson and Riggins (16), and Rist (17) show far more tuberculosis in the initially negative reactors.

These results are outlined as extracted from the Prophit Survey (18) in England. The sequence has been rearranged by the present writers.

One of the present writers (T. L. B.) in an earlier report (2) found 8 cases of tuberculosis in the negative reactors compared to one in the "positives" in a short term study of a few cases. But the accumulation of cases of tuberculosis and the passage of time in follow-up has shown a constant leveling off of differences in the two groups over the years. The three year training period has become an artificial unit of time for observation in such studies as this. The tu-

berculin test remains the diagnostic standard for the presence or absence of tuberculous infection

The reason for the high morbidity in the "positive" group on entry is not clear. It seems most logical to account for it on the basis of the natural history of tuberculosis in young women, for the morbidity is normally highest in this age group. The peak of disease in this "positive" group lags behind that of the "negatives," nor is it at any time as high a rate. Removal of the more susceptible nurses with active cases of tuberculosis before they could apply for nursing school may account for this difference in the two curves of morbidity, but it seems an unimportant influence. Both groups had theoretically the same exposure to tubercle bacilli during their training, with working hours and living

TABLE 11\*

OBSERVER	YEAR	GROUP	FIRST EXAMINATION TUBERCULIN POSITIVE			FIRST EXAMINATION TUBERCULIN NEGATIVE		
			Total	Cases TB	Per cent	Total	Cases TB	Per cent
Shipman & Davis (5)	1933	Nurses	96	7	7.3	47	2	4.3
Pollack & Cohen (12)	1941	Nurses	419	7	1.7	280	5	1.8
Israel et al (14)	1941	Nurses	360	34	9.4	277	34	12.3
Geer (6)	1934	Nurses	87	1	1.1	204	8	3.9
Hembeck (15, 16)	1936	Nurses	625	20	3.2	412	57	13.8
Amberson & Riggins (17)	1936	Nurses	285	2	0.7	207	6	2.9
Rist (18)	1939	Nurses	84	0	0.0	60	6	10.0
Comparing this study Badger & Ayyazian	1948	Nurses	374	31	8.2	362	40	11.0

\* From the Prophit Survey (18)

conditions the same. Diet was fundamentally the same, subject to variations imposed by the idiosyncrasies of young women concerning their weight.

*Primary vs reinfection tuberculosis* The pathogenesis of tuberculosis has for many years been thought of in terms of primary or "childhood type" tuberculosis and reinfection or "adult type," each tending to be differentiated into its own rather characteristic clinical and prognostic pattern. Tuberculin and roentgenographic surveys of children and young adults during the past twenty years have conditioned our thinking in terms of tuberculin-negative and -positive reactors, again each with its own type of lesion. "Primary" or "childhood type" tuberculosis was pictured as occurring in non-reactors who turn positive, and "reinfection" or "adult type" tuberculosis as occurring in those who were already positive to tuberculin. Moreover, there has been a prevailing view that "primary" tuberculosis is a relatively benign disease compared to that of "reinfection" type.

Ghon (9) and Ranke (10) first wrote of "primary" tuberculosis as a "childhood" disease and "reinfection" tuberculosis as its "adult" form. Epidemio-

logic changes in the morbidity and mortality of tuberculosis have altered our attitude towards these earlier concepts, chiefly because large sections of the population now do not develop their first or "primary" infection until the second, third, or fourth decades of life

The Prophit Tuberculosis Survey (18), published in 1948, in its very interesting study of tuberculosis in the British Isles speaks of primary and reinfection disease as follows (paragraph 2, page 184)

It is recognized by all, except a few who believe that pulmonary tuberculosis in young adults is usually the result of a primary infection, that reinfection is responsible for much, or indeed most adult tuberculosis. The two terms, "adult" and "reinfection" tuberculosis, are used synonymously

Such conclusions are not in accord with our clinical observations, nor with recent pathological studies which will be described

Terplan (19), in his exhaustive pathological studies of human tuberculosis, presents the evidence for primary infections up to the age of 80 years. He shows that the pattern of healed primaries is the same for all age groups and exists in the lung parenchyma with and without regional lymphatic involvement. He feels that the development of tuberculin sensitivity should not be made the dividing line between "primary" and "reinfection" tuberculosis. Sensitivity to tuberculin occurs soon after the initial lodgement of tubercle bacilli in the body, but there is no sound basis for regarding a positive tuberculin test with the development of allergy as the criterion of "reinfection"

Lurie (20) in 1944 presented the results of years of experimental study with tuberculosis in numerous strains of inbred rabbits with *known* variations in their inherited constitutional resistance to tuberculosis. He found that there was *no* constant pattern of "primary" or "reinfection" tuberculosis. Those strains of rabbits with high resistance to tuberculosis could localize the naturally acquired primary infection in the lung parenchyma without any regional lymphatic involvement. But with similar exposure those with low natural resistance produced the familiar "primary complex" with regional lymph node involvement and infection in distant organs. A *single* artificial infection produced similar effects and different patterns of disease which varied according to the inherent resistance of the rabbit strain when the infecting doses were similar.

Medlar (21), in his pathological studies of *Primary and Reinfection Tuberculosis as a Cause of Death in Adults*, finds no clear-cut difference in the pathology of "primary" and "reinfection" tuberculosis in humans. He found the "primary" or first infection the usual cause of death from tuberculosis under the age of forty, but occasionally its cause up to sixty years. Beyond the age of forty, "reinfection" tuberculosis was more common. The term "reinfection" tuberculosis he uses only in the sense of a new infection from outside the body, new disease acquired in the presence of a former but obsolete and healed "primary." Thus, as Amberson points out, the differentiation of primary and reinfection tuberculosis is a pathological problem and not possible to distinguish clinically. But Medlar goes further in his pathological studies in feeling that



allergy does not play a very important part in determining the progress of the disease. He found primary and reinfection (in the strict sense) tuberculosis to be indistinguishable, on a pathological basis.

*Constitutional factors* It is not clear what makes "primary" or "first infection" tuberculosis in one individual go on to subclinical healing throughout its course, while in another the process becomes progressive cavernous disease, and in still another it progresses from early pneumonic consolidation to a rapid death. The clinical observations of this study point to the importance of inherent constitutional resistance as being one of the most important influences in establishing the course and prognosis of each case. All our nurses had the same theoretical exposure to sputum "positive" cases of tuberculosis during training and experienced similar living and working conditions. *It is of importance that the initially tuberculin-negative and -positive groups developed not only a closely similar amount of tuberculosis but developed disease which was clinically comparable in both groups as seen by similar roentgenograms, similar treatment, and similar end results.*

It is of interest also that among the negative reactors on admission 14 per cent went through training without ever becoming tuberculin-positive. Perhaps these individuals were endowed with a very superior resistance to tuberculosis which destroyed the tubercle bacillus before it could establish a "beach head" in the body. Perhaps they were just lucky. Eighty-six per cent of those who did turn positive showed no roentgenographic or clinical evidence of tuberculosis and exhibited the presence of acquired infection only by a positive tuberculin test. Fourteen per cent of those who did turn positive showed roentgenographic evidence of tuberculous lesions. In approximately one-quarter of this group the lesions remained subclinical throughout the period of roentgenographically demonstrable disease. These groups must all have been endowed with good resistance to their tuberculosis.

Clinically, it has seemed to us and has been noted previously (2) that the inherent constitutional resistance of the individual to tuberculosis was the most important factor in determining the pattern of her disease. Lurie (20) makes it clear from his experimental studies that "the resistance of rabbits to naturally or artificially acquired tuberculosis is a function of their genetic constitution."

Medlar (21) states that the cause for progression in some primary infections is due to inherent qualities of susceptibility of certain parts of the lung, the apices of the lobes, when infection lodges in those areas. Thus the additive effects of frequent re-exposure may lead to development of disease by the greater chance of apical involvement.

However the case may be, good mechanical technique for breaking contact and spread of tubercle bacilli should be established, but dependence upon these technical factors of prevention should not be exploited at the expense of other measures. No matter what mechanical or immunological procedures are used in prevention, constitutional resistance, general health, fatigability, diet and nutrition, the way of living and psychological reactions to family, work, and recreation, all play their part and contribute to the response of the host to infection.

Comparison of our results with those of other similar studies carried on for fifteen years or more shows expected differences Heimbeck in 1947 (23) reported a twenty year follow-up of his nurses at Ullevål Hospital, summarized under "Foreign Letters" in the Journal of the American Medical Association (23) His reported results are as follows

	NUMBER NURSES	NUMBER CASES OF TUBERCU- LOSIS	DEATHS
Pirquet Positive	668	35	1
Pirquet Negative (BCG Vaccination)	501	42	5
Pirquet Negative (No BCG)	284	105	12

The above figures represent the accumulated results of his group of nurses during their three year training period only His "second period" of observation includes the accumulated data of the seventeen years following completion of training In this second group it is reported that there was essentially no difference in the morbidity or mortality in the above three groups of nurses

The high incidence and high mortality rate in his "negative" unvaccinated nurses seems to indicate some racial differences in a greater susceptibility to tuberculosis in Norwegian nurses The "positives" on entry to training suggest a true "survival of the fit" with earlier elimination of the susceptibles by the Darwinian process of "natural selection" Their exposure to tuberculosis must have come before they reached the age for training as nurses Again in the unvaccinated "negatives" on entry, with their high morbidity and mortality, those susceptible to tuberculosis were eliminated under observation Those who survived did as well in subsequent years as the "positives" on entrance to training This would be expected

This study of Heimbeck's has shown the usefulness of BCG vaccination in his nurses where results point to a racially greater susceptibility to tuberculosis and where the high morbidity and mortality suggest more severe disease and a greater risk of exposure to bacilli The differences in results of these two long follow-up studies may well be explained on this analysis of racial and individual variations in constitutional factors

*Morbidity* The morbidity or case rates of this study compare favorably with that of other reported series Childress (24) in his fifteen year study found an annual attack rate of 1.39 per 100 in student nurses Amberson and Riggins (4) in a shorter study present a rate of 1.09 per 100 per year for over-all lesions, but 0.68 per hundred nurses per year for new pulmonary and pleural lesions requiring treatment Our rate for new pulmonary and pleural lesions requiring treatment in the longer fifteen year follow-up was 0.73 per 100 per year, approximately the same as that of Bellevue, another large municipal hospital This rate of 0.73 per 100 nurses per year for us is higher than that recorded in Childress' article (24), for clerks in the Metropolitan Life Insurance Company in New York of 2 to 3 per 1,000 per year, or 0.2 to 0.3 per 100 per year The latter value, however, is similar to our annual rate of 0.2 per hundred after graduation

It is believed that the length of our follow-up and the absence of other life tables outside the nursing profession of similar length does not permit a satisfactory comparative study. Our rates do, however, present a definite trend over the years and the long term picture is favorable. The attack rate at the time of highest known exposure, during training, is proportionately higher than during the post-training period. But the early discovery of the minimal lesion by routine six-month roentgenographic examinations shows 89 per cent of the nurses with arrested lesions, and working or living a normal life.

In a hospital community where control against contact with the tubercle bacillus has not been elaborate but basic, it appears that many factors already outlined contribute to the development of clinical tuberculosis, in addition to contact with the microorganisms. It is not enough to consider the individual lesion alone during the time a nurse is in training. In this study the detailed analysis of the progress of the disease is considered in the light of further understanding the pathogenesis of tuberculosis from clinical experience. The perspective granted by the fifteen year follow-up emphasizes the excellence of late results and the importance of the inherent constitutional capacity of young women to handle tuberculous infections successfully, when diagnosed and treated in the earliest stages.

#### SUMMARY

1 Seven hundred and forty-five nurses followed five to fifteen years have shown statistically the same amount of tuberculosis appearing in the initially negative and positive tuberculin reactors.

2 The findings offer little justification for any clinical differentiation into "primary" or "childhood" and "reinfection" or "adult" tuberculosis. The type of disease has been essentially the same in character, course, and prognosis in both groups.

3 The individual, inherent, constitutional resistance to tuberculosis has clinically seemed the most important single factor in determining the pattern of disease in this group of nurses over the years. Their similar age, sex, living and working conditions, their similar diet and exposure to tuberculosis have been fairly constant. Individual differences in the course of similar types of lesions have borne very little relationship to the duration or degree of allergy.

4 A discussion of primary or reinfection tuberculosis has led us to the conclusion that most, if not all, of the disease in this group has been primary, first infection tuberculosis, whether it appeared in the initial reactor or non-reactor to tuberculin.

5 These studies have shown that the first infection, or "primary" tuberculosis, as seen in the initially negative tuberculin reactors, may go on to progressive destructive tuberculosis of almost any type. It may, in the other extreme, become rapidly arrested with clearing of the shadow on the roentgenogram and at no time give constitutional or local signs or symptoms of clinical tuberculosis. All gradations of the disease may appear between these extremes. The tuberculosis which appeared in the initially positive reactors acted in the same man-

ner Thus the state of allergy appears to play less part in the pathogenesis of the disease than do inherent constitutional differences in resistance to tuberculosis, together with environmental factors and treatment

6 The morbidity of this group compares favorably with that observed in other similar series The final rate for all lesions is 93 per 100 nurses per year, while the rate for new pulmonary and pleural lesions needing treatment is 73 per 100 nurses per year

#### SUMMARY

#### *La Tuberculosis en las Enfermeras Observaciones Clínicas sobre su Patogenia segun Revelan Quince Años de Vigilancia de 745 Enfermeras*

1 Setecientas cuarenta y cinco enfermeras observadas de cinco a quince años han revelado sustancialmente la misma proporción de tuberculosis en las negativas y las positivas inicialmente a la tuberculina

2 Los hallazgos ofrecen poca justificación para la diferenciación clínica en tuberculosis "primaria" o "infantil" y de "reinfección" o "adulta" La forma de la enfermedad fué esencialmente idéntica en naturaleza, evolución y pronóstico en ambos grupos

3 La resistencia constitucional, inherente, individual a la tuberculosis pareció ser el más importante factor aislado en lo tocante a determinar el patrón de la enfermedad en este grupo de enfermeras a través de los años La semejanza en edad, sexo, condiciones de vida y de trabajo, alimentación y exposición al mal fué bastante constante en ellas Las diferencias individuales en la evolución de lesiones de forma semejante guardaron poquísima relación con la duración o la intensidad de la alergia

4 Un estudio de si la tuberculosis era primaria o de reinfección lleva a la conclusión de que la mayor parte de la enfermedad, sino toda, en este grupo ha sido primoinfección, ya apareciera en las inicialmente negativas o positivas a la tuberculina

5 Estos estudios demuestran que la primoinfección, o tuberculosis "primaria, tal como se observara en las inicialmente negativas a la tuberculina, puede avanzar a tuberculosis destructora progresiva de casi cualquier forma Por otro lado, puede también estacionarse rápidamente con despejo de la sombra radiográfica sin manifestar en ninguna ocasión signos o síntomas orgánicos o locales de tuberculosis clínica Entre esos extremos pueden presentarse todos los grados de la enfermedad La tuberculosis que apareció en los reactores inicialmente negativos actuó en la misma forma El estado de alergia parece, pues, desempeñar en la patogenia de la dolencia un papel menor que las inherentes diferencias orgánicas en la resistencia a la tuberculosis, unidas a los factores del ambiente y al tratamiento

6 La morbilidad en este grupo compárase favorablemente con la observada en otras series semejantes El coeficiente final para todas las lesiones fué de 0.93 por 100 enfermeras por año, en tanto que para las nuevas lesiones pulmonares y pleurales que necesitan tratamiento es de 0.73 por 100 enfermeras por año

*Acknowledgments*

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Reports and roentgenograms from Middlesex County, Plymouth County, Rutland State Sanatoriums, the Boston Sanatorium, and the Channing Home for Tuberculosis, as well as numerous Veterans Administration hospitals, contributed greatly to the completeness of the study. To all these we are greatly indebted for their assistance.

We are grateful to all the nurses whose loyalty to the study and whose repeated responses over the fifteen years have enabled us to fit the pieces of this picture puzzle together.

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APPENDIX  
Table of Case Histories  
Summaries

CASE NUMBER	DIAGNOSIS	LESION SIZE IN CM	SYMPTOMS		PHYS- ICAL SIGNS	RA- CILI	TREATMENT	PROGRESSION REACTIVATION	END RESULT
			Con- stitu- tional	Local					
Initially negative reactors									
1 R I A	F A	Bilateral cavity	+	+	+	S +	Pneumothora bilateral	Progression	Died
2 D A	Min	1 5 by 2	0	+	0	G +	Rest, home	0	A W
3 J F A	Min lym- phatic	1 by 2	0	0	0	0	Rest, 12 months	Reactivation Pleural ef fusion	A M 3 Ch
4 L B	Min	3 by 2	+	0	0	+	Rest (O R A A ) 3 times	Reactivation 3 times	-M 1 Ch
5 R L B	Min	1 by 1 5	+	0	0	0	Rest, 6 weeks	0	A W
6 G McD B	Min	1 by 2	0	0	0	0	O P D only	0	A M 1 Ch
7 G F C	Min	2 by 3	+	+	0	0	O P D only	0	A M 3 Ch
8 M H C	Min	1 by 1	+	0	0	+	Rest, 5 months Pneumo- thorax Re-expan sion 1941	Progression 1 year	A W
9 A R C	Min	3 by 3	0	0	0	0	O P D only	0	A M 2 Ch
10 J C	Min	1 by 2	+	0	0	0	Rest, 6 months	0	Under treat ment
11 M H D	Min	2 by 2	+	0	0	0	Rest, 6 months	0	A M 1 Ch
12 E D	Pleurisy with Ef- fusion		+	+	+	0	Rest, 6 months	0	A M Acci- dental death
13 M R D	M A	Bilat	-	-	-	0	Rest, years	Reactivation Kidneys, spine	Under treat- ment A M 1 Ch
14 D D	Min	1 by 1 5	0	0	0	0	O P D only	0	A W
15 V C F	Min	1 5 by 2	0	0	0	0	Rest, 10 weeks	Reactivation Pleural ef fusion	A M
16 E M F	Min	3 by 4	+	+	+	?	Pneumothorax Re-expansion ?	0	A W M 3 Ch
17 C G	Min	3 by 4				0		0	A W
18 V G	Min	3 by 4	0	+	0	0	Rest, 9 months	0	A W
19 H U K	Min	3 by 3 5	0	0	0	0	O P D only	0	A M
20 B M	Min	1 by 1	0	0	0	0	Rest, home	Reactivation 5 months rest	A W
21 M M	Min	1 by 1	0	0	0	-	Rest 6 months	Reactivation 6 months rest	A
22 G B M	Min	2 5 by 3	+	0	+	G +	Pneumothorax Re-expansion 1945	Reactivation	A M 3 Ch

Table of Case Histories—Continued

CASE NUMBER	DIAGNOSIS	LESION SIZE IN CM	SYMPTOMS		PHYS- ICAL SIGNS	BA- CILLI	TREATMENT	PROGRESSION REACTIVATION	END RESULT
			Con- stitu- tional	Local					
Initially negative reactors—Continued									
23 H F M	Pleurisy with ef fusion		+	+	+	0	Rest, 2 months	0	A M 1Ch
24 E M	Min *	1 by 1 5	0	+	+	0	O P D only	Reactivation Pleural Ef fusion	A W
25 H M C	Min *	1 by 1	0	0	+	0	Rest, 6 months	Reactivation Pleural Ef fusion	A W
26 H D Mc C	Min	2 by 3	+	0	0	—	Rest, home	0	A M 3 Ch
27 J M	Min	1 by 2	+	0	0	0	Rest 6 months	0	A W
28 E M	Pleurisy with Ef fusion		+	+	+	—	Rest, 6 months	0	A W
29 K M	Min	1 by 2 5	+	0	0	+	Rest, 2 months San O R A A	Reactivation	Under treat- ment
30 R H O	M A	4 by 5 Cavity	+	+	+	+	Pneumothorax collapsed	0	Under treat- ment M 3 Ch
31 R G O'R	Min	2 by 3	0	0	0	0	O P D only	0	A M 1Ch
32 M R	Min	2 by 2 5	0	0	0	0	Rest 6 weeks	0	A W
33 M R	F A	1 5 by 2	++	+	++	++	Pneumothorax bilateral	Progression	Died
34 P S	Min	L U L	+	0	0	0	Rest, 12 months	0	A
35 A M S	Min	2 5 by 2 5	+	+	+	—	Pneumothorax Re-expansion 1948	Reactivation	A M 1 Ch
36 H S	Plourisy with Ef fusion		±	0	+	0	O P D plus rest	Reactivation A S	A W
37 C I S	Min	2 by 2	0	0		G +	O P D Pneu- mothorax Reexpansion	Reactivation	A M 1 Ch
38 M C S	Min	1 by 2 5	0	0	0	0	O P D only	0	A M 2 Ch
39 T T	Min	3 by 4	0	0	0	0	Rest, 6 months	0	A W
40 G H W	Min	2 by 1	0	+	0	0	Rest, 2 months	Reactivation Pleural effusion	A M
41 N E A	Tuberculous adenitis		0	+	0	Bi- opsy prov- en	O P D only	0	A M
42 F B	Min	2 5 by 1 5	0	0	0	0	Rest, 3 months	0	A W
43 B C B	Min	1 by 1	0	0	0	0	Rest, 4 months	0	A M 3 Ch
44 C O B	Min	1 5 by 0 5	+	0	0	0	Rest, 5 months	0	A M
45 M A C	Min	1 5 by 2 0	+	0	+	0	Pneumothorax Re-expansion 1945	Reactivation A S	A W
46 G S C	—	—	—	—	—	S +	?	Rapid pro- gression	Died—TB M



Table of Case Histories—Continued

CASE NUMBER	DIAGNOSIS	LESION SIZE IN CM	SYMPTOMS		PHYS- ICAL SIGNS	BA- CILLY	TREATMENT	PROGRESSION REACTIVATION	END RESULT
			Con- stitu- tional	Local					
Initially positive reactors—Continued									
47 E P C	M A	5 by 6 Pneumonic	+	+	+	G +	Pneumo <sup>o</sup> horax Bilateral re- expansion 1947	Progression ± 3 yrs	A M
48 M J C	M A *	Left lung	+	+	+	S +	Thoracoplasty, left	Reactivation, Pleural ef- fusion	A
49 C C	Min	2 by 3	+	+	+	—	Pneumothorax collapsed	Progression	Under treat- ment
50 M C	Min	2.5 by 3	+	+	+	S +	Rest, Sanatori- um O R A A	Reactivation	Died hemor- rhage
51 M K D	Min	1 by 3	+	+	0	S +	Rest, 6 months Thoracoplasty	Reactivation	Under treat- ment M
52 B M D	Min	2 by 3	0	0	0	0	Rest 6 months	0	A M 2 Ch
53 M D	M A	6 by 7	0	+	+	0	Rest 4 months	0	A W
54 B F	Min	1.5 by 1.5	0	0	0	0	Rest, 4.5 months	0	A M
55 L K H	Min	1.5 by 3	0	0	0	0	O P D only	0	A M 1 Ch
56 A C H	Min	1.5 by 2	0	0	0	0	O P D Pneu- thorax	Reactivation	A W 1 Ch
57 M H	M A	Bilateral apex	+	+	+	+	Sanatorium 6 years Pneu- thorax 6 years Re-expansion, 1943	Progression	A W
58 J K	M A	R L L Calc ++	0	0	0	0	O P D only	0	A W
59 H K	Min	L U L 2 by 3	+	+	+	0	Rest 3 months	Reactivation Pleural ef- fusion 1942 TB Salpgrts 1947	A M
60 G S L	Min	1.5 by 5.5	0	+	0	0	O P D only	0	A M 1 Ch
61 G K M	Min	6 by 8	+	+	+	—	Pneumothorax Re-expan- sion 1945	Progression	A M
62 T McI	M A	Right lung	+	+	+	S +	Pneumothorax collapsed	0	Under treat- ment A A
63 A McL C	Min	Bilateral apex	+	—	—	—	Pneumothorax Re-expan- sion 1945	0	A M 1 Ch
64 M R M	M A	7 by 11	+	0	0	—	Rest, eight months O R A A	0	A M 2 Ch
65 I G O	Min	9 by 2.5	+	0	0	—	O P D only	Reactivation	A M 1 Ch
66 F W I	Min	1 by 1.5	0	0	0	0	O P D only	0	A M 1 Ch
67 F A I	Min *	1 by 2	+	+	+	—	Rest 4 months	Reactivation Pleural ef- fusion	A W
68 M G P	Min	1 by 1	0	0	0	0	O P D only	0	A M 2 Ch

Table of Case Histories—Concluded

CASE NUMBER	DIAGNOSIS	LUNG SIZE IN CM	SYMPTOMS		PHYSICAL SIGNS	BA CELLS	TREATMENT	PROGRESSION REACTIVATION	END RESULT
			Constitutional	Local					
Initially positive reactors—Concluded									
63 M F G	Min	15 by 25	+	0	0	—	Pneumothorax Re-expansion 1946	Reactivation	A W
70 F V	Min	1 by 2	+	0	0	0	Rest 4 months	0	Under treatment
71 C W	Min	2 by 2	+	0	0	—	Pneumothorax Re-expansion 1947	Progression	A

*Index*

- A = Arrested  
 M = Married  
 W = Working  
 O P D = Out Patient Department follow up only  
 Post = Post treatment only  
 Ch = No of children  
 \* = With pleurisy with effusion  
 O R A A = Own risk against advice (discharged)

# THE PROBLEM OF TUBERCULOSIS CONTROL AMONG AMERICAN NEGROES<sup>1 2</sup>

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## INTRODUCTION

The problem of tuberculosis control among United States minorities is difficult to discuss. Minorities do not exist here in a European sense. Economic, cultural, ethnic, and language barriers do not completely dissociate any group from the population as a whole. All types of tuberculosis may be found in all segments of the population without regard to ethnic origins or other outward characteristics which might distinguish individuals as members of special groups.

This discussion, therefore, will be concerned with trends in groups which are identifiable as different from the white majority on the basis of evident physical characteristics. The impossibility of making subtle scientific distinctions among individuals in gathering the basic data from which statistics are compiled imposes a practical limit upon our ability to draw fine conclusions. Considerations which affect the severity of tuberculosis among Negroes may be useful in planning the protection of the entire population.

## THE NATURE OF THE PROBLEM

*Death rates.* In the United States registration area in 1910 the death rate from tuberculosis among the white population was 148.3 per 100,000 and among the Negro population the rate was 447.7 per 100,000. In 1945, after 35 years, the U. S. Public Health Service reports a rate of 32.7 per 100,000 for whites and 98.0 for Negroes. The ratio of white to Negro death rates remains at 1.3 despite the dramatic decline recorded for both groups. A greater disparity in death rates exists between 15 and 44 years of age where the Negro rate exceeds the white by five times (1).

The death rate for some other United States minorities is higher than that for the entire nation. Chinese, Japanese, Indian, Eskimo, Porto Rican, and Mexican-American rates are reported to be high (2).

The proportionate mortality from tuberculosis in major cities for 1945 shows the largest disparity between white and non-white deaths in the 15 to 24 year age groups. The severity of tuberculosis for non-whites appears to increase with the size of cities. The tuberculosis proportionate mortality is highest in Northern industrial cities (3).

*The prevalence of pulmonary tuberculosis.* The prevalence of tuberculous disease among Negroes does not exceed that among whites to an extent comparable

<sup>1</sup> From the Division of Chronic Pulmonary Diseases, Howard University School of Medicine, Washington, D. C.

<sup>2</sup> Presented before the Southern Tuberculosis Conference in Savannah, Georgia, October 2, 1948.

to the excess of mortality. Some surveys have actually shown a *smaller prevalence* of tuberculosis among Negroes even though the *death rate* exceeded that for whites by six or more times. Edwards reports this in his exhaustive report of mass surveys in Harlem (4). Comparable observations are reported by other observers (5, 6).

We are, therefore, confronted with the fact that pulmonary tuberculosis, while not more prevalent among American Negroes than among whites, is a more severe and more rapidly fatal disease. This has been confirmed in numerous studies (1, 7, 8, 4, 9).

*The extent of infection.* The extent of infection by tubercle bacilli in terms of the relative percentages of tuberculin-positive persons in non-white and white groups in the various localities is of importance here. New York City figures reported by Drolet in 1934 were 47.9 per cent positive tuberculin tests in young Negroes below age 15 and 52.1 per cent positives for young whites of a similar age. Death rates, however, were 10 times as high for this group of Negroes as for whites (10). A similar finding, although infection was more prevalent, was reported from the Phipps Institute in 1928 for South Philadelphia high school children (11). Whitney and McGaffrey reported a national prevalence of positive tuberculin reactions for whites of 46.5 per cent and 47.8 per cent for Negroes. Whites experienced a one per cent per year of age average increase in reactors and Negroes an increase of 0.5 per cent. The increase before age 20 was *more rapid* for Negroes.

Although approximately equal percentages of tuberculin sensitivity have been indicated for the white and non-white groups in many studies, it is possible that infection falls with different emphasis upon the non-white groups. A more rapid increase in positive reactors in the younger age groups in Negroes has been mentioned. Furcolow and others report a great disparity between positive reactors in Negro and white school children in Kansas City which would indicate that in this city, at least, Negro children below 18 are more frequently infected with tubercle bacilli than whites (12).

Although further studies are required at present, it may be assumed that the annual incidence of tuberculous infection is greater for Negroes below age twenty.

*The concept of race.* Differences in recorded vital and morbidity statistics have given rise to many theories concerning the influence of race-specific factors upon the severity of tuberculosis. This concept requires clear analysis. In a scientific sense, the Negro minority in the United States is not an ethnic entity (13, p. 136). The Negro is identified by skin color, other physical characteristics, or by descent from persons of African stock. These characteristics identify Negroes in the statistics of human welfare. The same factors set Negroes apart from the white majority in the cultural, economic, occupational, educational, and political life of all sections of this country. Such differences are not biological. It is, therefore, exceedingly difficult to base scientific conclusions concerning tuberculosis upon the common designation of race.

The variable factors which operate upon the non-white minority in contrast to the white would have to be strictly controlled in order to observe the single

and distinct influence of the predominant racial stock upon the tuberculosis epidemic

The decline of the Negro tuberculosis death rate to less than 25 per cent of that for 1900 is difficult to explain as the operation of an inheritable disease-resisting factor. That the white death rate is now 16 per cent of that for 1900 does not imply the special operation of a factor linked to race. The differences in rate of decline may result from the influence of the peculiar economic, occupational, and cultural structure of American society.

If a racial or genotypic factor be eliminated as the sole reason for the differences in response to tuberculosis between whites and Negroes, we may hope for a solution in practical measures.

*Epidemiologic and immunologic considerations* The observation that tuberculosis of the lung is a more severe disease in the non-white minority demands interpretation. If the explanation is to be found in the physical and environmental factors, these should bear with peculiar emphasis upon the Negro. Some whites should also be affected in proportion to the operation of adverse influences upon them.

Rich (14) has stated that the extent and destructiveness of a lesion which will develop in a given tissue within definite time after inoculation is increased by the virulence and number of bacilli.

The effect of this inoculum is also enhanced by the hypersensitivity of the host organism.

The destructive effects of these factors are modified by resistance which is both native and acquired. This relationship is expressed in quasi-mathematical form as

$$L \text{ is equivalent to } \frac{V \times N \times H}{R(n + a)}$$

Influences which tend to increase the effect of the numerator in this expression would, therefore, increase the severity of the lesions. Influences which diminish the effects of the denominator would act similarly. Since lesions are admittedly severe among the non-white minority, some factors on the right of this expression must, therefore, operate with peculiar severity among non-whites and not to such a large extent among whites.

*The virulence and number of bacilli* Since the bacilli causing pulmonary tuberculosis in this country are not confined to the majority or minority by physical barriers, their virulence can be assumed to be the same for all groups.

The number of bacilli involves (a) a large single inoculum occurring as the result of a single exposure, (b) repeated inoculations in several exposures over a period of time.

Do these factors operate with greater severity among non-whites?

A group not generally educated to sanitary and hygienic practices may experience inoculation with larger numbers of tubercle bacilli with greater frequency than a better trained group. Conceivably, the more customary communal use of personal articles, a carelessness about personal contacts, and ignorance of the

dangers of contagion may lead to the more frequent infection of the non-white minority with large bacillary inocula

Sterner Associates tabulate findings of the Federal Housing Administration which are shown in part in table 1

These studies indicate substandard sanitation for a significantly greater proportion of Negro families in all areas of the country. The extent of overcrowding is severe for Negroes and much greater than for whites. In Detroit, for instance, 16 per cent of all dwelling units reported occupied by Negroes housed more than two persons per room against 0.4 per cent of the dwellings occupied by whites. The report also indicates that in urban areas in 1930, 29 per cent of Negro families had lodgers as against only 10 per cent of white families. The propor-

TABLE 1  
*Comparison of Housing Facilities for Whites and Negroes*

CITY	YEAR OF STUDY	PERCENTAGE OF DWELLING UNITS IN NEED OF MAJOR REPAIR OR UNFIT FOR USE	
		Negro	White
Hartford, Conn	1939	29.9	2.5
Buffalo, N. Y.	1939	36.2	8.9
Philadelphia, Pa.	1939	22.9	3.5
Harrisburg, Pa.	1939	72.8	12.6
Detroit, Mich.	1939	33.7	6.8
Alexandria, Va.	1936	66.5	14.8
Birmingham, Ala.	1939-1940	56.5	19.7
New Orleans, La.	1939-1940	46.8	14.1
Atlanta, Ga.	1939	59.2	21.6

tion of broken families was reported as approximately 10 per cent higher for Negroes than for native whites (15)

Poor housing, overcrowding, and then associated social and economic stresses operate with unique severity upon the Negro. Is it not conceivable that these conditions added to the other consequences of a low living standard may operate to increase the number and frequency of inoculations with tubercle bacilli for a larger proportion of Negroes?

The frequency of large inocula in the early decades of life may result from poor physical conditions of existence, a slower acquisition of the principles of hygienic living, and possibly from traditional employment in personal service capacities. The occurrence of rapidly progressive disease is, in itself, presumptive evidence of more intensive exposure to tubercle bacilli (16)

That family or household contact is less frequently detected among Negroes with tuberculosis points to heavy extra-domestic exposure. Whites may experience a larger number of slight casual contacts to account for the presence of infection when observed.

Hypersensitivity to the tubercle bacillus is difficult to measure. Work done at Phipps Institute suggests that Negroes react more frequently to the smallest

dose of PPD tuberculin and that the frequency of severe reactions is greater. At Howard University some 630 positive tuberculin reactors were found prior to 1910. Of these, 75 per cent reacted to the first dose of PPD (17).

A direct relationship appears to exist between numbers of bacilli inoculated and the severity of anaphylactic sensitization. Hypersensitivity is, therefore, increased with the number of bacilli and with greater frequency of inoculation. If Negroes experience larger and more frequent bacillary inocula, we may then account in large part for a greater degree of hypersensitivity.

The observed decrease in tuberculosis death rates in this country has accompanied an improvement in the physical conditions of living, in sanitation, in knowledge of hygiene, and in conditions of work. Minority groups have enjoyed these improvements to an appreciably lesser extent than the majority and consequently tend to experience more intensive exposure at earlier ages.

The slighter inoculation of bacilli among the majority resulting from less intensive exposure tends to produce active immunity or slowly progressive lesions when they occur. The more intensive inoculation in the non-white group produces progressive tuberculosis earlier in life or leaves foci which produce progressive disease in later life.

*Resistance* Resistance to tuberculosis is a complex factor. It is not a measurable quantity. Its presence must be inferred from the reactions of tissues and organs to infection. It is a variable which may be lessened by any number of transient or persistent influences. Some of these factors may exert large general effects and so must be considered.

*Species or racial resistance* Immunity is postulated upon the basis of observed tissue responses in experimental animals of many species and strains. Comparison of these pathological changes has been the basis for rating human individuals as resistant or susceptible. This analogy is accurate within limits. The conditions under which human infection may occur can hardly be duplicated for animals. The differences between human ethnic groups are not analogous to those between different species such as white mice and guinea pigs. The familial immune traits demonstrated to exist in rabbit families may exist in humans (18). We can safely assume, however, that a great many years would pass before humans could significantly "breed out" a comparable genetic trait which controls lack of resistance to tuberculosis.

Bogen (19) reports that the death rate from tuberculosis among Australians has been the lowest in the world since records have been kept. These people left England originally during a period of high death rates when racial immunity, if it existed, would be thought low. Americans migrating from England about the same time experienced extremely high death rates. The Australians have enjoyed favorable death rates, however, despite a low bed-to-death ratio. Since they have not lost large portions of population from tuberculosis, the killing off of susceptible strains cannot be presumed to account for the present favorable rates.

That there is native resistance to tuberculosis cannot be denied. That this resistance is linked directly to ethnic traits or that it has been influenced by

natural selection in our present society is not proved. Large scale deficiencies in the resistance to tuberculosis of non-white minorities cannot yet be scientifically explained as a race-specific phenomenon.

*The influence of age.* Resistance to progressive tuberculosis is a characteristic which appears to increase with age. Nevertheless, Chadwick (20) quotes Frost as pointing out that the group aged 50 to 60 in 1930, if followed back to birth, actually experienced the highest mortality at ages 20 to 30 and that the high rates at the older ages are the residuals of higher rates in early life.

Pinner (21, p. 199) stated, however, on the basis of autoptic experience, that the proportion of lethal or severe tuberculosis to total tuberculosis appears to decrease with age. This observation may be confirmed in any large scale chest roentgenogram survey by a comparison of the incidence of symptomatic active lesions per thousand to the proportion of total reinfection infiltrates in the various age groups examined. In Howard University students, the ratio of progressive reinfection lesions to total lesions has been thought a significant guide to show sex and age probability of progression (22). This ratio, if it can be applied, may supply concrete evidence of age-specific resistance to tuberculous progression. Since infection with large inocula may appear earlier in minorities, the importance of developing such an index is obvious.

Resistance varies with a number of physiologic phenomena associated with sexual maturation, childbearing, and other developmental and aging factors. These influences would seem to be equally influential in all groups and would assume added importance in a minority only when operative at an age during which heavy exposure is frequent.

*Nutrition.* Resistance to progressive tuberculosis appears to vary with the standard of living of the individual or groups (23). This is a complex influence in which many subfactors may operate. Of these, poor nutrition seems most important. The influence of nutrition upon the various elements of the population is inadequately studied. No extensive body of evidence is available to show the influence of deficient nutrition during the period of most active growth upon the ability to develop and maintain resistance to tuberculosis in later life.

The effect of extreme malnutrition upon tuberculous disease in concentration camp inmates in Germany appears to produce autoptic appearances similar to those reported by Pinner and Kasper in Negroes (24). A large incidence of lymphogenous and blood-borne tuberculous metastases and remarkably severe liver damage is reported (25).

Faber reported from Denmark in 1938 that low protein nutrition was one of the factors accounting for the spectacular increase in tuberculosis in the first world war (26). Pinner states that no other nutritional factor plays such a decisive role as protein in influencing the epidemic behavior of tuberculosis (21, p. 520).

Poor nutrition operates especially among Negroes. Myrdal states, upon the basis of 1941 Department of Agriculture studies, that "the majority of the Negro population suffers from severe malnutrition" (13, p. 375). Thus he attributes in part to poverty and in part to "cultural factors" influencing the



choice of foods. The influence of diet upon resistance to tuberculosis is obvious, especially since costly protein is one of the notoriously deficient items reported in the dietary.

Wari, metabolic diseases, and intercurrent infections would appear to act equally upon resistance in all groups and to exert no special influence upon the problem at hand.

*Acquired resistance.* Koch demonstrated that the inoculation of previously healthy animals with a pure culture of tubercle bacilli excited, after ten to fourteen days, a changed reactivity which was accompanied by the development of an immune reaction which reached its optimum in four to six weeks. The development of this immune reaction, however, depends upon the size of the initial inoculum and upon the frequency of inoculation in the ten to fourteen day preallergic phase. If the inoculum is large or frequently repeated, the allergic phase develops but progressive tuberculosis occurs, denoting an overwhelming of the host prior to the development of the immune response.

Holm has noted a comparable phenomenon in the natives of Bornholm, Denmark who, being largely tuberculin-negative, develop progressive tuberculosis when they migrate to the urban Danish mainland. Ferguson reports a similar situation among tuberculin-negative native white nurses exposed to open tuberculosis in Canadian hospitals.

*Massive inoculation* with human tubercle bacilli may result either in immediately progressive disease or in the development of foci which progress to an extent depending upon the speed with which resistance or acquired immunity develops.

The speed of fission of bacilli in large inocula may be assumed to exceed the speed of development of immunity which may at any point modify the resulting lesion to varying degrees of chronicity (27). Casual or slight exposure later in life, however, seems far more likely to produce an immune reaction which inhibits progression of the primary inoculum or its satellites and may impose chronicity or healing upon these or subsequent inocula.

The protection of experimental animals by small inocula of tubercle bacilli has been demonstrated by many workers. The controlled administration of small amounts of avirulent tubercle bacillus has been demonstrated to cause the development of acquired immunity. The occurrence of small inocula of virulent bacilli might be responsible for the development of relative immunity among United States whites. Large inoculations with virulent bacilli are expected to occur more frequently in Negroes. Acquired immunity should develop more effectively in the less intensely exposed group.

#### WHAT NEEDS TO BE DONE FOR TUBERCULOSIS CONTROL AMONG THE NEGRO POPULATION

Known factors increase the severity of tuberculous disease among the Negro population in the United States. No special or unusual influences need be postulated to account for higher death rates. The thorough application of familiar community tuberculosis control programs to the entire population is of the

greatest urgency. The official and voluntary health organizations must enlist the participation of everyone.

The problem of tuberculosis among Negroes cannot be isolated in our thinking or planning. Emphasis should be placed on some special aspects of this problem.

1 *Research*. A program of research should be planned in order to study and identify the environmental, cultural, economic, and educational factors which may adversely influence the resistance of Negro Americans to tuberculosis. The program should include the following features:

- (a) Modern methods of social research should be employed by trained social scientists to identify these environmental factors. Objective medical study should then be able to demonstrate statistically significant, physiologic, or pathologic variants produced by social and economic influences.
- (b) Up-to-date information concerning the prevalence of tuberculous infection is needed. This should be specified for age, race, sex, and locality.
- (c) Age-specific ratios between the incidence of frankly active pulmonary tuberculosis and that of all forms of pulmonary tuberculosis should be formulated from the largest possible chest roentgenogram survey experiences in each community. These ratios may be expected to indicate the age-specific expectancy of progressive tuberculosis for all elements of the population.

2 *Improved medical care*. The more rapid progression of pulmonary tuberculosis in the non-white makes it imperative that minor pulmonary infiltrates and early minimal tuberculosis be treated more effectively and vigorously by every medical and surgical means at our disposal.

The prevention of contagion by the earliest possible recognition and treatment of progressive disease is a medical and public health obligation which is obviously of particular importance.

3 *Isolation of open cases*. The early and effective isolation of "tubercle bacillus" carriers is necessary in *all groups* of our population. A program of good medical care should motivate the individual acceptance of isolation with a hope for recovery.

4 *Economic provisions for the tuberculous*. Early hospitalization, medical care, and isolation should be made possible by two strong steps:

- (a) The means test should be abolished as a requirement for tuberculosis hospital treatment. No citizen should be *forced* to expend savings in order to undergo treatment for the general good of the community.
- (b) Adequate financial assistance should be given to the families of tuberculous breadwinners during hospital treatment and convalescence. This would bring tuberculosis patients in marginal economic groups under earlier medical care and result in shorter hospitalization and earlier return to work.

5 *Educational improvement*. Every educational channel available should be devoted to the ideal of educating all Americans to the best standards of living, of hygienic practice, of nutrition, and of conditions of work. The general adoption of such standards will speed the acquisition of the cultural traits required to counteract the effects which reduce resistance.

A more general understanding of the harmful effects of urban and rural slums

upon national health will, it is hoped, lead eventually to intelligent attacks upon these problems

6 *BCG vaccination* BCG vaccination offers hope of developing a useful degree of acquired resistance in the younger age groups of the Negro population. The complexity of the factors producing increased susceptibility to progressive tuberculosis makes it imperative that we do not rely on this measure alone.

7 *Ancillary medical procedures* The fullest possible assistance in the measures outlined above must be sought from the techniques of medical social work, public health nursing, vocational rehabilitation, and voluntary tuberculosis agencies. These services are essential to the support of the prophylactic and therapeutic programs. Their general adoption must be supported.

#### SUMMARY

1 Tuberculosis is a more severe disease among the non-white minority in the United States than for the majority.

2 The factor of race in the ethnic sense plays only a small part in identifying the Negro in the United States. Cultural, occupational, economic, and educational limitations set the non-white group apart. A biological explanation of the observed severity of tuberculosis in a group not biologically defined is not consistent with logic.

3 Environmental conditions increase the severity with which tuberculosis strikes. The number and severity of bacillary inocula are greater for a group which experiences to a greater extent than another the disadvantages of crowding, unsanitary environment, and social disorganization.

Hypersensitivity develops more strongly as a consequence of larger inocula with more bacilli. Resistance of the natural type depends on good nutrition and age of first intensive exposure. These two factors are demonstrably unfavorable to the maintenance of resistance in a large portion of the Negro minority. Acquired resistance develops following an inoculation with tubercle bacilli in an optimum dose. Massive or frequent inocula may cause hypersensitivity and, on a purely mathematical basis, may enable bacillary growth to outstrip the development of acquired immunity. This favors the development of progressive tuberculosis.

These factors are susceptible of demonstration and do not require the invocation of race-specific phenomena as speculative influences. Research to determine the specific physiologic consequences of environmental and nutritional deficiencies is much needed.

#### SUMARIO

*El Problema de la Lucha Antituberculosa en las Minorías de los Estados Unidos*

1 La tuberculosis es una enfermedad más grave entre las minorías no blancas de los Estados Unidos que entre la mayoría de la población.

2 El factor raza en su sentido étnico sólo desempeña un pequeño papel en lo tocante a definir el estado de la minoría que no pertenece a la raza blanca, que queda también separada del resto de la población por limitaciones culturales,

vocaciones económicas y educativas. Toda explicación biológica de la notoria gravedad de la tuberculosis en un grupo biológicamente indefinido resulta ilógica.

3. Las condiciones del medio acrecientan claramente la intensidad con que hiera la tuberculosis. Las que concebiblemente intervienen en una gran proporción de las minorías son:

- (a) La cantidad y la gravedad de los inoculos bacilares son mayores en un grupo que experimenta en mayor grado que otro, las desventajas creadas por el hacinamiento, la miseria y la desorganización social.
- (b) La hipersensibilidad se desarrolla más poderosamente a consecuencia de inoculos mayores con más bacilos.
- (c) La resistencia de tipo natural depende, entre otras cosas, de la nutrición y de la edad al tener lugar la exposición. Esos dos factores son notoriamente adversos al mantenimiento de la resistencia en una gran proporción de la minoría negra.
- (d) La resistencia adquirida se desarrolla consecutivamente a la inoculación de bacilos tuberculosos en dosis óptima. El exceso o la frecuencia de los inoculos pueden provocar hipersensibilidad, pero a base puramente matemática, pueden hacer que la proliferación bacilar retrague el desarrollo de la inmunidad adquirida. Esta situación favorece la aparición de tuberculosis progresiva.
- (e) Postulase, pues, que la lesión tuberculosa será más grave en la población negra por hallarse una proporción mayor de ese grupo expuesta a la inoculación masiva, y por lo tanto al desarrollo de hipersensibilidad. Los factores del medio ambiente contribuyen a esa situación. Postúlase también que la resistencia natural de una gran proporción de los negros sería baja debido al mal estado de su nutrición y a su exposición a una edad menor a la dolencia. La resistencia adquirida no se manifiesta tan rápidamente en la minoría por agobiar la intensidad de la exposición el organismo antes de que aquella pueda ocurrir.

Estos factores son susceptibles de demostración y no requieren la invocación de fenómenos etnoespecíficos como causas hipotéticas. Hay mucha necesidad de estudios que determinen las específicas consecuencias fisiológicas de las deficiencias del medio ambiente y de la nutrición.

#### *Acknowledgment*

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# STREPTOMYCIN THERAPY OF TUBERCULOUS PNEUMONIA IN NEGRO ADULTS<sup>1</sup>

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## INTRODUCTION

Tuberculous pneumonia is considered a major indication for streptomycin therapy.<sup>2,3</sup> This extensive cavitative type of pulmonary tuberculosis is seen in various and grave form in Negroes, and was an almost universally fatal condition prior to the advent of streptomycin. The present report is a description of the results obtained in the 15 Negro adults with tuberculous pneumonia who were treated with streptomycin on the Stanford Service of the San Francisco Hospital from 1946 to 1949. Much has been learned from these cases about the management of tuberculous pneumonia, and it is felt that application of the principles which have emerged from this study should produce more favorable results in the future.

## OUTLINE OF THE STUDY

The Negro adults included in this study varied in age from 18 to 45, 8 were women, and 7 men. All were hospitalized during streptomycin therapy and were kept on bed rest except for such minor privileges. Because of the serious nature of the illness, the patients remained in the hospital for considerable periods following cessation of antimicrobial therapy. Streptomycin was administered for two to four months in doses of 1.0 Gm. daily, which was usually given in two injections at twelve-hour intervals. Other measures, including various forms of collapse therapy and other surgical procedures, were performed as they seemed indicated before, during, or after streptomycin therapy.

The diagnosis of tuberculous pneumonia was made on the basis of extensive, confluent cavitative pulmonary disease in patients manifesting considerable fever and toxicity. Plethomorphic infiltrations which cleared rapidly and were presumably caused by the aspiration of blood were not included.

## OBSERVATIONS AND RESULTS

*Group 1—Patients in whom there was improvement, followed by relapse.* In 11 of the 15 patients there was an initial period of improvement, followed by relapse. As indicated in table 1, 1 of these patients died, and it is likely that most if not all of the remaining 7 will eventually succumb to the disease.

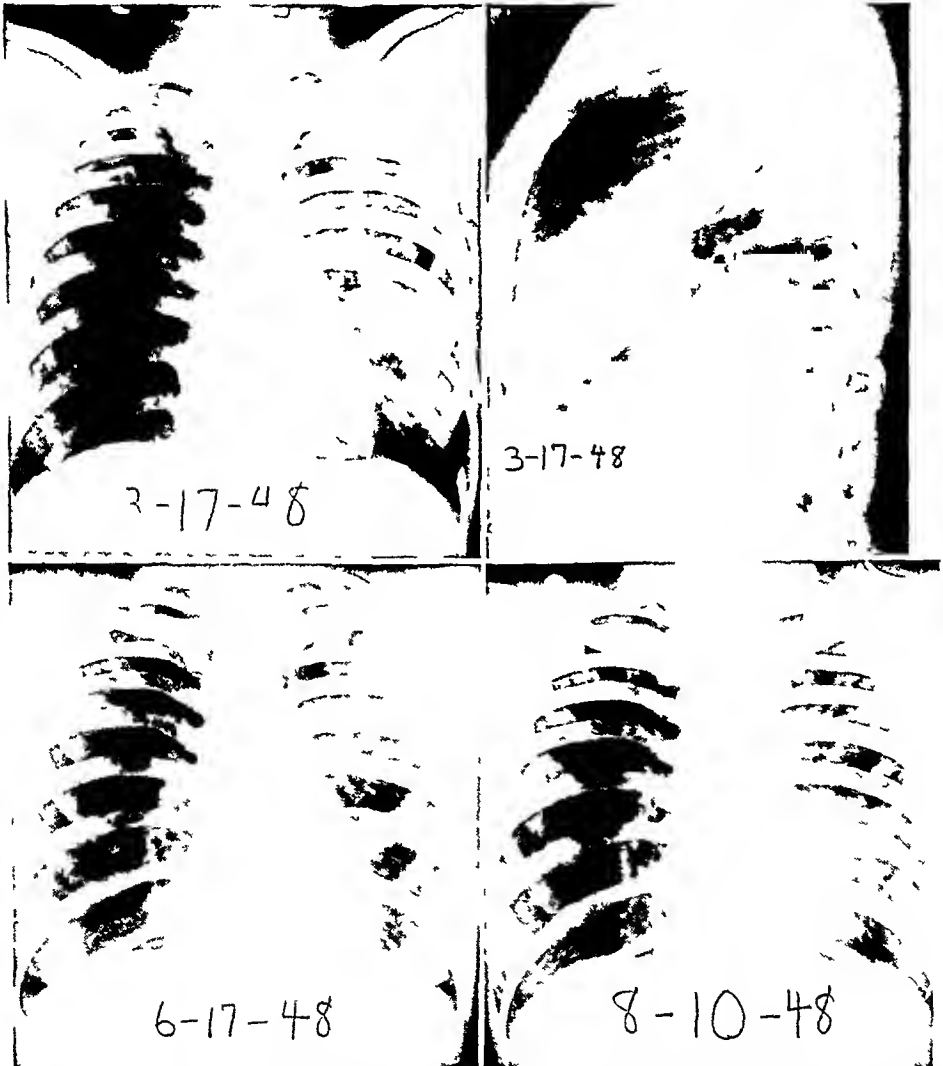
A typical example of the course of events occurring in this group is shown in figure 1. The patient was a 23-year-old colored housewife who had been acutely ill with tuberculous pneumonia for two months prior to the administration of streptomycin. Symptomatic improvement was noted within a few days after starting therapy, and within two weeks the temperature, which had been rising to 102°F daily, gradually returned to normal. During the two months of strepto-

<sup>1</sup> From the Department of Medicine, Stanford University School of Medicine, the Stanford Tuberculosis Service, San Francisco Hospital, and the San Francisco Department of Public Health.

TABLE 1

Results in 15 Negro Adults with Tuberculous Pneumonia Who Were Treated with Streptomycin

		NUMBER OF PATIENTS
Group 1	Improvement, followed by relapse	11
	Living 7	
	Dead 1	
Group 2	Improvement, no relapse	4



FIGS 1 A and B (Upper left and right) Patient A B Chest roentgenograms before treatment Note the confluent exudative disease, located chiefly in the left upper lobe, clearly outlining the oblique fissure

FIG 1 C (Lower left) Film taken 10 days after end of two month course of streptomycin, showing some clearing of the parenchymal infiltrations A large cavity is now visible in the left first interspace

FIG 1 D (Lower right) Enlargement of the cavity and progression of the disease on the left, with the appearance of infiltrations in the right fourth interspace Patient died two months later

mycin therapy she gained 10 pounds and her cough and sputum were greatly diminished. At the end of the treatment period, however, the sputum remained positive for tubercle bacilli and the organisms cultured were highly resistant to streptomycin. Because of the presence of empyema in the left first interspace, a thoracoplasty was scheduled. Within two weeks after discontinuing streptomycin, however, her temperature again became elevated and her condition deteriorated so rapidly that the operation was never performed. Streptomycin was again started but within five days she became almost totally deaf and the drug was discontinued. She died four months after completion of the first course of streptomycin therapy.

A similar case is illustrated in figure 2. This 15 year old, colored male had had cough, fever, and left chest pain for one month, during which he lost 30 pounds. During a three month course of streptomycin therapy he became afebrile and gained 15 pounds. Thoracoplasty was scheduled, but within two weeks after cessation of streptomycin his fever returned and he began to lose weight. Tubercle bacilli obtained at this time grew in the presence of 10 % per cent of streptomycin but were inhibited by 100 %. Streptomycin was given for a second two month course but his condition grew steadily worse and he died two months after completion of the second course.

The chest roentgenograms of a third patient in this group are presented in figure 3. This 27 year old, colored male was thought to have a nontuberculous bacterial pneumonia in October 1946 on the basis of cough, sputum, right chest pain, and right upper lobe infiltration on the roentgenogram. He was treated by a private physician but failed to improve, and in April 1947 he was admitted to a nearby sanatorium with tuberculous pneumonia. He had lost 25 pounds and was very ill. Pneumoperitoneum was instituted and he received streptomycin for eleven weeks from July to September 1947. During this period he showed marked symptomatic improvement and gained 5 pounds, but his condition became worse almost immediately after antimicrobial therapy was discontinued. He was transferred to the San Francisco Hospital in January 1948 where pneumoperitoneum was continued, but the situation was obviously hopeless and the patient died four months later.

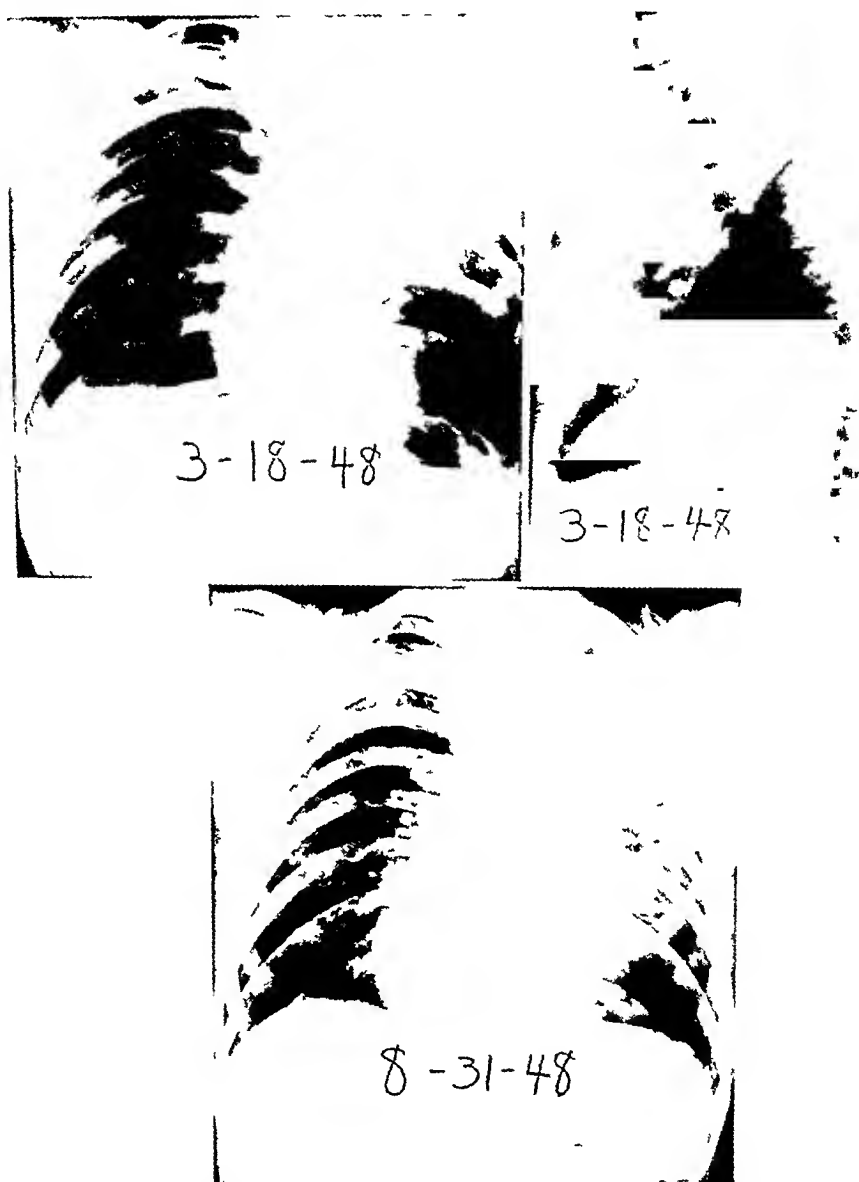
The course in the other 8 patients in this group was strikingly similar to that which occurred in these 3 patients. In 5, some form of collapse therapy was administered, but in every instance it was inadequate to control the disease. Three patients received both pneumothorax and pneumoperitoneum. One patient received a 2 stage thoracoplasty, but the cavities were not closed by this procedure and she is steadily getting worse.

*Group 2. Patients showing improvement, without relapse.* In contrast to the 11 patients in Group 1, the results in the 4 patients comprising Group 2 have been highly satisfactory to date. Since the objective of this study is to discover factors which are of importance in bringing about a favorable therapeutic result, these 4 cases will be presented briefly. Two received pneumoperitoneum in addition to streptomycin, and 2 had pneumonectomies.

One of the most striking responses occurred in a 26 year old male, whose



films are presented in figure 4. He had been ill for ten weeks prior to streptomycin therapy, with cough, sputum, fever, abdominal cramps and diarrhea. His



FIGS 2 A and B (Upper left and right) Patient S. H. Chest roentgenogram one week before starting streptomycin, showing extensive exudative disease with cavitation, confined chiefly to the left upper lobe

FIG 2 C (Lower) Film two months after the first course of streptomycin showing spread and further excavation. The infecting organisms were resistant, and the patient pursued a progressively downhill course despite a second course of streptomycin therapy

temperature, which was 104°F, fell to normal during the first month of treatment, the gastro-intestinal complaints disappeared, and he gained 30 pounds

Pneumoperitoneum was started two weeks after completion of the ninety day course of streptomycin. Sputum and gastric cultures have been negative for

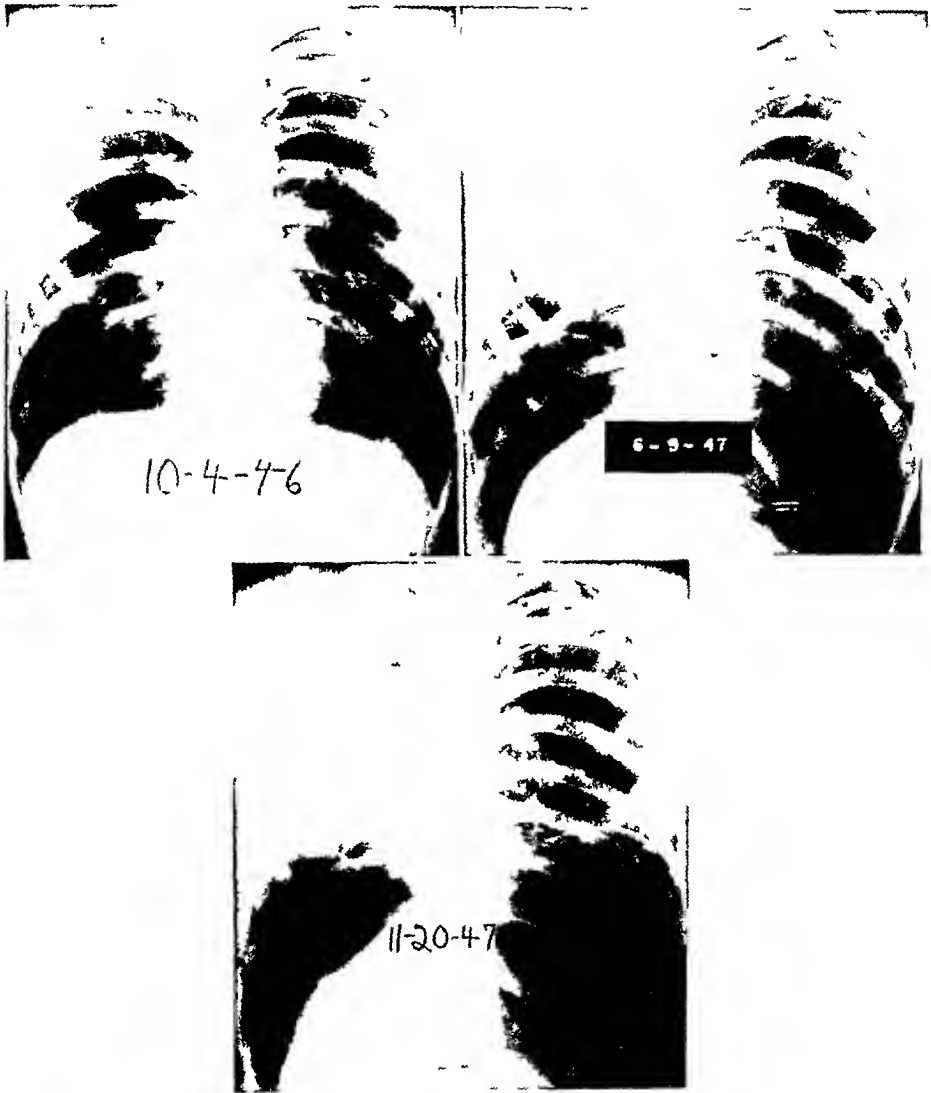


FIG 3 A (Upper left) Patient E. P. Roentgenographic appearance at the time a diagnosis of "pneumonia" was made

FIG 3 B (Upper right) Condition a month after pneumoperitoneum was instituted, and three weeks before streptomycin was started. There is now an extensive tuberculous pneumonia of the right lung

FIG 3 C (Lower) Film taken two months after streptomycin was discontinued, showing progression of the disease with extensive cavitation. Death occurred six months later

tubercle bacilli since the second month of streptomycin therapy. In view of the sudden onset, the bilaterally symmetrical chest lesions, the gastro-intestinal lesions, the prompt "conversion" of the sputum, and the lack of definite cavi-

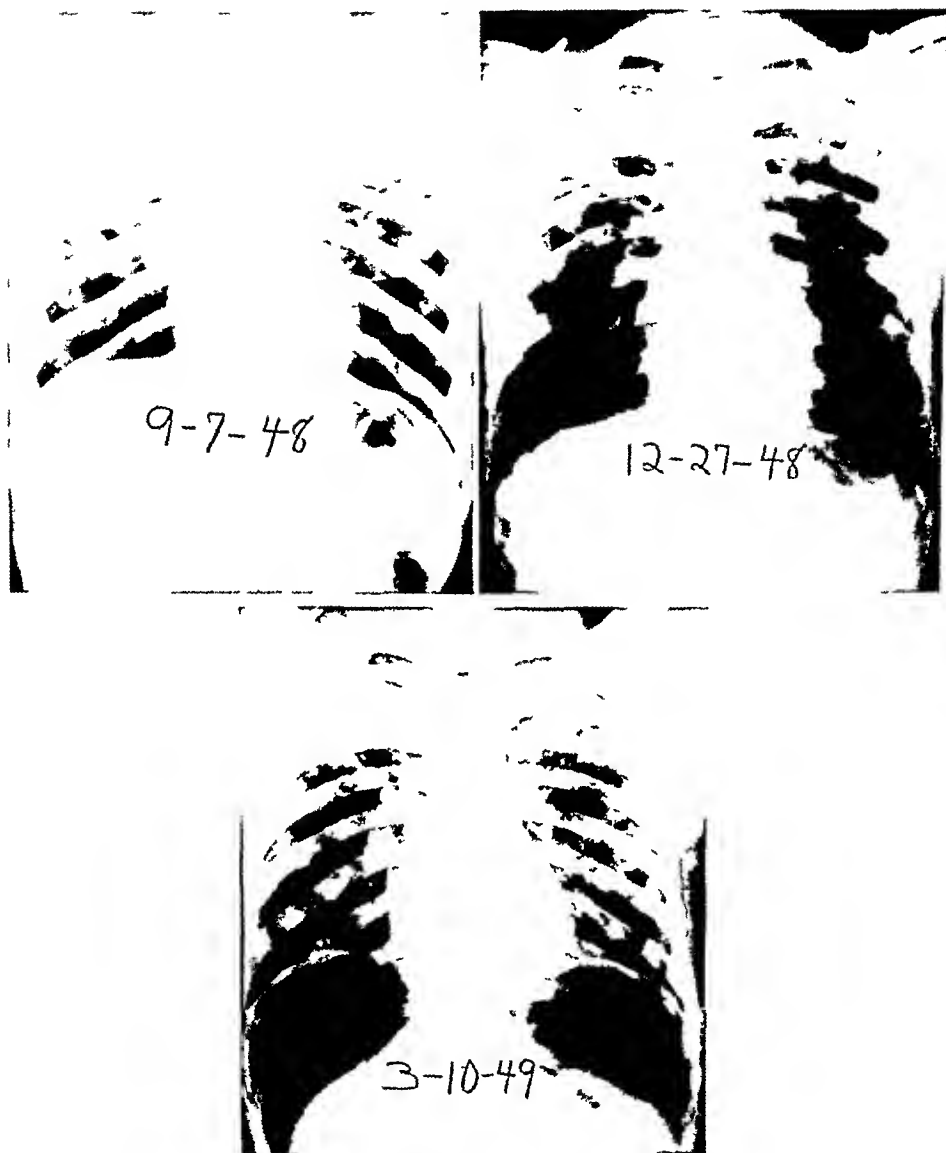


FIG 4 A (Upper left) Patient E. H. Extensive bilateral exudative disease ten days before streptomycin was administered. This may have been hematogenous in origin.

FIG 4 B (Upper right) Marked regression of the pulmonary infiltrations is seen eight days after the ninety day course of streptomycin therapy.

FIG 4 C (Lower) Further regression is noted 2 months after starting pneumoperitoneum. In spite of the suggestive cavitation in both first anterior interspaces, sputum and gastric cultures have been repeatedly negative.

tion, it is possible that the disease in this case may have been hematogenous in origin. If so, the predominately interstitial character of the lesions may account in large part for the favorable response obtained.

The other patient who received pneumoperitoneum was a 22 year old house-

wife with a left lower lobe pneumonia which showed considerable progression during the first five weeks in the hospital, before streptomycin was administered (figure 5). A 3 cm cavity, with a fluid level, could be faintly visualized above



FIG 5 A (Upper left) Patient L. W. Pneumonitis, left lower lobe, with a 3 cm cavity just above the diaphragm

Fig 5 B (Upper right) Marked spread of the tuberculous pneumonia, left lower lobe, six weeks later and twelve days before streptomycin was started. Patient was quite toxic and febrile at this time

FIG 5 C (Lower) Film taken fourteen weeks after discontinuing streptomycin, and twelve weeks after starting pneumoperitoneum. There has been marked clearing of the pneumonia, and the cavity is apparently closed. Note the calcifications in the spleen

the left diaphragm in the first film. Streptomycin was given in daily doses of 1.0 Gm for ninety days, and two weeks later pneumoperitoneum was instituted. She gained 20 pounds and sputum and gastric washings became negative for tubercle bacilli during the second month of streptomycin therapy. Six months

following the completion of antimicrobial therapy, she is showing continued improvement, and the plan is to continue pneumopneumothorax for several years.

Two patients have recently been observed in whom a more aggressive approach seemed indicated. The first of these was an 18 year old housewife who was three months pregnant when she entered the hospital in September 1948,

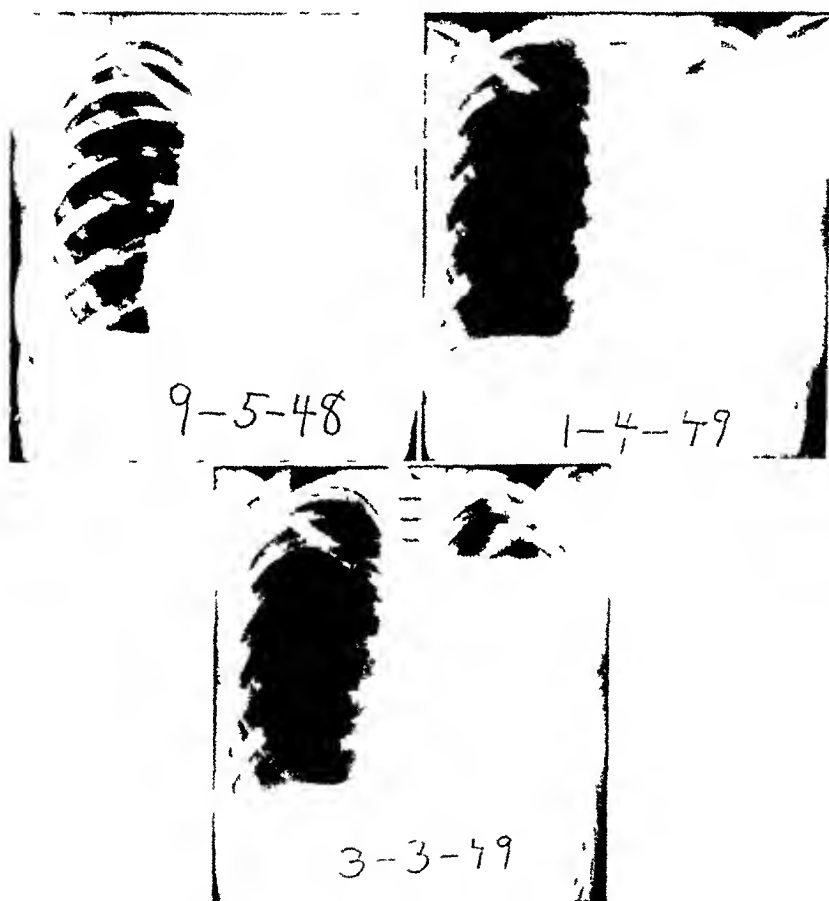


FIG 6 A (Upper left) Patient B.S., with extensive involvement of the left lung. She was three months pregnant at this time.

FIG 6 B (Upper right) Film taken ten days following completion of the first course of streptomycin, showing some clearing but extensive excavation.

FIG 6 C (Lower) Appearance seven weeks after starting the second course of streptomycin, and five weeks following left pneumonectomy.

with an extensive tuberculous pneumonia of the left lung (figure 6). Although she had a daily temperature elevation to 102°F or higher and had lost 15 pounds, she showed a surprising lack of awareness of her symptoms. She was placed on streptomycin September 30, 1948, and two days later the pregnancy was interrupted by abdominal hysterotomy. There was a weight gain of 13 pounds during three months of streptomycin therapy, but at the end of treatment she still had a daily fever of 99.5°F. Realizing that her course without further treatment

would be like that of the cases in Group 1, a second course of streptomycin was started January 19, 1949, and left pneumonectomy was performed January 29,



FIG 7 A (Upper left) Patient M. E. Right upper lobe cavity of seven months duration with a fluid level present

FIG 7 B (Upper right) Infiltration throughout the right lung four days after the sudden emptying of the cavity contents into the right bronchial tree

FIG 7 C (Lower left) Extensive tuberculous pneumonia, right lung, three weeks after starting streptomycin, and three days before right pneumonectomy

FIG 7 D (Lower right) Film taken seven weeks after right pneumonectomy

1949. The postoperative course was uncomplicated. At present, two months after the operation, she is afebrile, her sputum and gastric washings are negative

for tubercle bacilli on smear and culture, and she is gaining weight. She refuses thoracoplasty, but a permanent left pleural interruption is scheduled. The follow-up period is too short to predict the eventual outcome, but the outlook so far is certainly favorable as compared with the first 11 patients. It is of particular interest that a sensitivity test started before the pneumonectomy, but reported a month after the operation, showed the organisms to be resistant to 1,000  $\gamma$  of streptomycin per cc. of medium.

The second case was a 39-year-old housewife who was found to have a tuberculous cavity of the right upper lobe in late 1917. By May of 1918, despite right pneumothorax and pneumoperitoneum the cavity was still open and it contained a fluid level. On May 15, 1918, the cavity contents suddenly flowed into the right lung, causing an extensive spread of the disease. During the next six months she lost 35 pounds and ran a downhill febrile course. Because her condition was considered desperate, streptomycin therapy was started December 16, 1918 and a right pneumonectomy was performed January 8, 1919. The postoperative course was stormy for two weeks, but since then she has been afebrile and two months after the operation has gained 5 pounds. Several sputum smears and gastric cultures, since surgery, have been negative for tubercle bacilli. She refuses thoracoplasty. Again, the follow-up period is very brief, but the situation seems encouraging and the condition certainly would have terminated fatally without surgery.

#### COMMENT

Certain general principles concerning the management of tuberculous pneumonia seem apparent in viewing the results obtained in this series. Beneficial effects of streptomycin were noted in every case, as manifested by marked symptomatic improvement, decline in fever, diminution of cough and sputum, and gain in weight. The improvement was only temporary, however, unless streptomycin therapy was combined with adequate collapse measures. The extensive, destructive nature of the disease, with its widespread tissue necrosis and cavitation, was such that streptomycin alone caused only temporary suppression of the process and relapse and progression followed within a few weeks. Similar experiences have been described by others (2).

Collapse therapy or other surgery was instituted in 12 patients, but in only 4 did it aid in controlling the disease. Artificial pneumothorax was attempted in 3 cases, but, in keeping with the usual experience in tuberculous pneumonia, it was unsuccessful. Pneumoperitoneum appeared to exert a beneficial effect in 2 cases (figures 4 and 5). In one of these a 3 cm. cavity overlying the left diaphragm was apparently closed, and in the other the sputum became negative for tubercle bacilli and cavitation was no longer demonstrable. Pneumoperitoneum was administered at some time to 9 patients, but the amount of collapse produced was not adequate to control the extensive exudative and cavity disease. The one patient who received a thoracoplasty had several large cavities which were not closed by the procedure, and her condition has steadily deteriorated since the operation.

The 2 patients in whom pneumonectomies were performed had predominately unilateral disease of the sort which had invariably terminated fatally in previous cases. The follow-up period has been short, but the results so far are encouraging and it is felt that an aggressive approach is indicated in this type of case. It is possible that the patients shown in figures 1, 2, and 3 might all have been saved if lobectomies or pneumonectomies had been performed at a judicious time.

It is evident then that the aim should be to provide adequate collapse therapy or other surgical measures and that these must be appropriately timed in relation to the streptomycin therapy, and particularly to the development of streptomycin-resistant infections. Two patients in the present series relapsed following streptomycin before a scheduled thoracoplasty could be performed. Generalizations concerning the type of collapse are not warranted, each case must obviously be decided on its own merits. In a disease as malignant as tuberculous pneumonia in Negroes, it is too much to hope to salvage every case. It would appear, however, on the basis of what has been learned in this study, that thoughtful planning and careful timing should make it possible to increase appreciably the percentage of cases permanently benefited.

#### SUMMARY AND CONCLUSIONS

Sustained improvement has been noted in 4 of 15 Negro adults with tuberculous pneumonia treated with streptomycin, relapse occurred in the other 11 following an initial period of improvement. Properly timed, adequate collapse therapy or other surgical procedures appear to be essential adjuvants to streptomycin administration in bringing about permanent improvement in this form of pulmonary tuberculosis, which is so highly fatal in Negroes. The early post-operative course has been encouraging in 2 patients with predominately unilateral disease in whom pneumonectomies were performed.

#### SUMARIO Y CONCLUSIONES

##### *Estreptomycinoterapia de la Neumonía Tuberculosa en Negros Adultos*

En 4 de 15 negros adultos con neumonía tuberculosa tratada con estreptomina notóse mejoría sostenida, en tanto que en los otros 11 un período inicial de mejoría fué seguido de recaída. Cronológicamente coordinados, la colapsoterapia adecuada u otros procedimientos quirúrgicos parecen ser coadyuvantes esenciales de la estreptomycinoterapia para obtener mejoría permanente en esta forma de la tuberculosis pulmonar, que es tan letal en los negros. En 2 enfermos con enfermedad de predominio unilateral en quienes se ejecutaron neumonectomías, la evolución postoperatoria temprana ha sido alentadora.

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# THE EFFECT OF ANTIHISTAMINE MEDICATION ON THE TUBERCULIN REACTION IN CHILDREN<sup>1</sup>

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## INTRODUCTION

The literature of late has had several articles attesting to the effectiveness of antihistamine agents in partially or completely inhibiting histamine wheals, allergic wheals, and passive transfer wheals. Typical of such reports is one by Ehas and McGavick (1), in which nonallergic patients were subjected to histamine skin tests before, during, and after oral administration of Benadryl. A definite diminution in both wheals and erythema was noted after three days of oral treatment with 100 mg of the drug daily. Arbesman *et al* (2) observed similar results using a dosage of 50 to 100 mg of oral Pyribenzamine and skin testing with histamine or allergens (ragweed, timothy, et cetera) forty-five minutes later.

It is surprising that, despite the widespread interest in the effects of the antihistamine agents on allergic manifestation, very little has been reported on the effect of these drugs on so common a reaction as the tuberculin test which is generally regarded as allergic in nature. Boquet (3) tested the action of several antihistamine agents on the intradermal tuberculin reaction in guinea pigs and was unable to find any inhibiting effect. R. W. Sarber (4), on the other hand, reports positive results on the tuberculin reaction in guinea pigs. He administered Benadryl subcutaneously in a dosage of 50 mg per Kg to 30 guinea pigs in which tuberculin sensitivity had been induced by the intraperitoneal injection of a suspension of mixed human and bovine strain of tubercle bacilli. The conclusions reached by Sarber are that in adequate dosage levels Benadryl causes a reduction in the tuberculin skin reaction and markedly reduces the incidence of necrosis in guinea pigs. On the basis of these findings he states that it is important to determine whether an individual being tested is receiving any antihistamine compound at the time of tuberculin testing before correct interpretation of a negative reading can safely be made. A search of the literature failed to reveal any similar careful studies performed on humans.

In the present study observations have been made on the effect of orally administered Tripeleminamine Hydrochloride (Pyribenzamine Hydrochloride-Ciba) on the tuberculin reaction in 43 children known to be positive reactors to tuberculin.

## METHOD OF INVESTIGATION

The study was conducted at the Prendergast Preventorium for Children. The substance used for intradermal testing was old Tuberculin, supplied by the Massachusetts Department of Public Health. To avoid the possibility of severe

<sup>1</sup> From the Prendergast Preventorium, Boston, Massachusetts.

# ANTI-HISTAMINE MEDICATION ON TUBERCULIN REACTION

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TABLE 1  
Tuberculin Reaction (1 100,000) with and without Pyribenzamine

	WITHOUT PYRIBENZAMINE		WITH PYRIBENZAMINE 60 MG DAILY FOR FOUR DAYS	
	Induration	Total erythema	Induration	Total erythema
	mm	mm	mm	mm
1 A S	12 by 12	33 by 22	14 by 14	12 by 26
2 D M	12 by 12	35 by 48	15 by 18	45 by 28
3 A T	20 by 20	28 by 20	10 by 12	32 by 44
4 R H	10 by 10	24 by 44	14 by 17	20 by 30
5 M H	12 by 17	18 by 26	10 by 14	30 by 42
6 K S	15 by 17	32 by 45	16 by 17	36 by 45
7 L W	10 by 10	40 by 15	15 by 16	45 by 40
8 K N	10 by 10	15 by 15	14 by 13	32 by 40
9 R D	10 by 10	25 by 28	10 by 10	23 by 23
10 E P	9 by 10	20 by 26	14 by 12	20 by 25
11 D W	10 by 10	15 by 20	12 by 13	20 by 28
12 P S	8 by 9	45 by 40	11 by 13	32 by 35
13 E B	15 by 20	22 by 30	16 by 16	25 by 40
14 D K	10 by 15	30 by 40	10 by 10	23 by 26
15 B M	10 by 10	20 by 25	14 by 14	30 by 38
16 S W	10 by 10	44 by 25	10 by 10	24 by 20
17 J G	15 by 15	17 by 35	12 by 15	40 by 44
18 M T	10 by 10	30 by 48	8 by 8	22 by 25
19 R D	15 by 15	25 by 25	10 by 10	30 by 46
20 T W	10 by 10	40 by 55	8 by 8	36 by 45
21 B N	10 by 10	22 by 30	14 by 16	15 by 20
22 S W	8 by 9	14 by 16	9 by 21	35 by 38
23 C D	10 by 20	20 by 50	6 by 6	23 by 35
24 D W	7 by 10	20 by 27	14 by 15	25 by 40
25 T D	8 by 6	25 by 35	10 by 12	22 by 30
26 J L	15 by 13	26 by 35	6 by 6	30 by 34
27 R B	17 by 12	45 by 33	10 by 12	25 by 25
28 V B	12 by 17	15 by 22	12 by 13	25 by 36
29 E J	10 by 12	14 by 20	6 by 6	32 by 48
30 P D	8 by 8	22 by 26	15 by 15	
31 V D	10 by 10	17 by 23	7 by 10	
32 V W	10 by 10	22 by 35	8 by 8	
33 P S	10 by 6	18 by 30	12 by 12	
34 W V	14 by 16	30 by 50	15 by 20	
35 M S	10 by 5	28 by 50	14 by 17	
36 R D	10 by 15	20 by 15	10 by 10	
37 J L	10 by 8	20 by 27	12 by 13	
38 L K	8 by 10			
39 C B	10 by 12			
40 F C				
41 D K				
42 A L				
43 W C				

reactions, and in an effort to obtain as nearly as possible threshold levels of tuberculin, a dilution of 1 100,000 (001 mg) was used. Forty-eight clear and definite reactions were read on the basis of the extent of induration and erythema after forty-eight hours.

Several days later 13 of the children, whose ages ranged between five and eleven years, were given Pyribenzamine in the dosage of 60 mg daily for two days before the tuberculin test was repeated. After the test, the Pyribenzamine administration was continued in the same dosage for another two days, at which

TABLE 2  
*Controls without Pyribenzamine*

	INDURATION	TOTAL ERYTHEMA	INDURATION	TOTAL ERYTHEMA
	mm	mm	mm	mm
1 N L	14 by 12	20 by 33	10 by 10	25 by 26
2 J D	10 by 10		7 by 10	26 by 32
3 F M	10 by 10	25 by 15	12 by 16	35 by 40
4 D G	18 by 25		10 by 11	24 by 34
5 J P	10 by 11	16 by 20		32 by 41

TABLE 3  
*Tuberculin (1 100,000) Reactions with and without Pyribenzamine*

	WITHOUT PYRIBENZAMINE		WITH PYRIBENZAMINE 2.0 MG DAILY FOR FOUR DAYS	
	Induration	Total Erythema	Induration	Total Erythema
	mm	mm	mm	mm
1 J G	10 by 10	20 by 25	16 by 20	37 by 70
2 B N	10 by 10	25 by 25	14 by 16	30 by 38
3 C D	10 by 10	22 by 30	15 by 15	24 by 25
4 J W	10 by 12	15 by 22	20 by 24	30 by 40
5 G K	10 by 5	18 by 30	15 by 20	
6 D K	10 by 8	38 by 30	17 by 21	42 by 50
7 A L	8 by 10	20 by 15	12 by 17	
8 F M	10 by 10	25 by 45	15 by 16	35 by 40
9 D G	18 by 25		10 by 10	24 by 40
10 J P	10 by 11	16 by 20	14 by 22	35 by 50

time a second reading was made (table 1). The remaining 5 children were not given Pyribenzamine but were retested with the others to act as controls of the intensity of the tuberculin reaction itself (table 2).

At a later date, 10 of the above children were again studied using larger doses of Pyribenzamine (240 mg daily for two days). They were retested with 1 100,000 tuberculin which was followed by two more days of Pyribenzamine in 240 mg doses before final reading (table 3). Here again a group of 5 children were tested as controls without receiving the antihistamine agent (table 4).

## RESULT

It may be seen from the data in tables 1, 2, 3, and 4 that Pyribenzamine, in the stated doses, had no inhibiting effect on tuberculin reactions in children. No toxic effects were noted from the medication. An interesting sidelight noted was that several of the children who received Pyribenzamine had marked relief from pruritus caused by insect bites and dermatitis venenata.

TABLE 4  
*Controls without Pyribenzamine*

	INDURATION	TOTAL ERYTHEMA	INDURATION	TOTAL ERYTHEMA
	mm	mm	mm	mm
1 R H	10 by 10	28 by 20	12 by 10	30 by 32
2 K S	10 by 10	18 by 26	8 by 15	24 by 48
3 R D	10 by 10	40 by 25	15 by 16	30 by 50
4 K N	10 by 10	15 by 15	18 by 20	
5 D W	10 by 10	20 by 26	10 by 11	24 by 47

## DISCUSSION

Although the various antihistamine drugs show considerable variation in their chemical structure, their therapeutic results, with the exception of side effects, are quite similar. It is probable, therefore, that these findings with the use of Pyribenzamine would have been repeated if any other antihistamine drug in the same comparative dosage had been used.

The fact that antihistamine drugs have no perceptible effect on the tuberculin skin test corroborates the views of Zinsser (5) on the nature of the allergic response involved in the development of the tuberculin skin tests. According to Zinsser there are two types of allergic responses on the part of the body to the tubercle bacillus and its products. One is an anaphylactic reaction, which is a protein reaction of the immediate edema-hyperemia (wheal type). The other is a tuberculin type reaction caused by the bacterial organism resulting in a delayed inflammatory reaction, causing more profound damage to the tissues.

The anaphylactic type reaction, according to Lewis (6), is caused by a histamine-like substance which is freed at the site of a local allergic reaction as a result of cellular injury. This histamine-like substance then reacts on the tissues to produce a characteristic "triple response": local dilatation of the small vessels, increased permeability, and diffuse dilatation of nearby arterioles. The classic example of this phenomenon is the resulting wheal when a specific antigen is introduced into the skin of an allergic individual and this reaction is inhibited by antihistamines.

In the tuberculin type reaction, it is probable that histamine does not play an important role. It is usually, although not always, dependent on the presence of tuberculous infection, is independent of anaphylaxis, and from the present findings is not inhibited by antihistamine medication.

## CONCLUSIONS

1 Pyribenzamine in an oral dose of 60 mg daily for four days had no inhibiting effect on the tuberculin reaction of 43 children ranging in age from five to eleven years

2 Pyribenzamine in an oral dose of 240 mg daily for four days had no effect on the tuberculin reaction of 10 children

3 In routine tuberculin testing one need not be concerned as to whether the patient is receiving Pyribenzamine, or any antihistamine medications, during the same period

4 It is believed that the observations presented are in agreement with the belief that a basic difference exists between tuberculo-allergy and tuberculo-anaphylaxis

## CONCLUSIONES

*Efecto de la Medicación Antihistamínica sobre la Reacción a la Tuberculina en los Niños*

1 La piribenzamina, a dosis oral de 60 mg diarios durante cuatro días, no ejerció efecto inhibidor sobre la reacción a la tuberculina en 43 niños de cinco a once años de edad

2 La piribenzamina, a dosis oral de 240 mg diarios durante cuatro días, no mostró efecto sobre la reacción a la tuberculina de 10 niños

3 En la comprobación corriente con tuberculina, no hay que prestar atención a si el sujeto recibe o no piribenzamina u otra medicación antihistamínica durante el mismo período de tiempo

4 Parece que los datos aquí ofrecidos confirman la creencia en una diferencia básica entre tuberculo-alergia y tuberculo-anafilaxia

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## CHEMOTHERAPY OF MURINE LEPROSY<sup>1,2</sup>

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### INTRODUCTION

The rapid development of chemotherapy in the past decade has stimulated renewed interest in the treatment of diseases caused by acid-fast organisms. Several of the recently developed therapeutic agents have been evaluated in leprosy, but few investigators have concerned themselves with therapy in experimental murine leprosy. Faget and his colleagues (1, 2) observed that human leprosy is benefited by treatment with either Promin or Diasone. Also Muir (3) reported favorable results from the use of Diasone. Few data are available on the therapeutic efficacy of the antibiotics. Penicillin was used unsuccessfully in the treatment of human leprosy by Faget and Pogge (4). The vagaries of Hansen's disease, however, make the evaluation of therapeutic agents difficult, and the chronicity of leprosy necessitates years of observation during which time many uncontrolled variables are introduced.

The need for an experimental animal to amass accurate data is urgent, but as yet no animal host has been found to be susceptible to *Mycobacterium leprae* of human origin. Murine and human leprosy are sufficiently similar, however, to consider possible the application of data from experimental chemotherapeutic studies of the murine infection to the disease in man. Although Fite (5) observed minor differences in the microscopic pathology of the two types of infection, it is still a matter of speculation whether they reflect differences in the host or the parasite. Few studies on the chemotherapy of murine leprosy have been carried out. A recent report by Cowdry and Ruangsiri (6), who employed Promin in the treatment of rats with well-developed leprous nodules, concluded that it had "no consistent effect" on the histologic structure of the lesion, although the general health of the animals was improved. Because of the paucity of data on the evaluation of recently developed therapeutic agents in murine leprosy and their possible use in human leprosy, the present investigation was undertaken to compare the therapeutic efficacy of Promin, Diasone, penicillin, and streptomycin, employing dosages equivalent to those recommended in man.

### MATERIALS AND METHODS

Two strains of murine leprosy were employed in the experiments. One strain, which has been carried through several passages in white rats in the laboratories of the Department of Bacteriology of the University of Rochester School of Medicine and Dentistry, was obtained

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from Krakower and Gonzalez (7) who recovered it from a mouse caught at the School of Tropical Medicine, San Juan, Puerto Rico. The other strain was supplied by Sellards of Harvard University approximately ten years ago and has been in experimental use ever since.

The inoculum was prepared from a subcutaneous leproma removed aseptically, placed in a sterile mortar, minced with scissors, and ground with alundum. Sufficient 0.85 per cent sodium chloride solution was added to obtain approximately a 20 per cent suspension. Films were then prepared from the suspension, stained, and observed to determine the relative number of acid-fast organisms.

Groups of from 10 to 20 white rats, Wistar strain, not over 3 months of age and weighing from 150 to 200 Gm., were inoculated subcutaneously with 0.2 ml. of the suspension rich in acid-fast bacilli. The usual site of injection was in the region of the right precaval lymph node. In each experiment a group of 5 rats was injected with inoculum that had been heated to boiling in a waterbath for ten minutes. The groups receiving this inoculum served as controls for possible nonspecific reactions due to either altered protein or to dead acid-fast bacilli and their products. All animals were maintained on a diet of Purina Fox Chow.

Therapy with Promin<sup>4</sup>, Diasone<sup>5</sup>, Penicillin<sup>6</sup>, and Streptomycin<sup>7</sup>, was carried out as follows. Approximately 50 mg. of Promin were fed daily in the diet for the duration of the experiment. It was prepared by adding 4 mg. of Promin to each Gm. of food, of which each rat consumed from 10 to 15 Gm. per day. One-half Gm. of Diasone per Kg. of body weight was injected subcutaneously daily for five months beginning the day of inoculation. The Diasone was dissolved in an 0.85 per cent saline solution. A single dose of 1,000 units of aqueous sodium penicillin was injected subcutaneously near the point of inoculation daily for five months. In the case of streptomycin, three treatment schedules were evaluated, 25,000, 50,000, and 100,000  $\gamma$  per Kg. of body weight daily. The streptomycin was injected at intervals of eight hours for five days, totaling 125,000, 250,000, and 500,000  $\gamma$  per Kg. of body weight.

The therapeutic efficacy of streptomycin was evaluated only in advanced murine leprosy, namely, an infection which had progressed six months and exhibited well-developed lepromata, and in some instances ulcers, at the site of inoculation. In this experiment, both the "Harvard" and the "Puerto Rican" strains were injected into the left gastrocnemius muscle of one group of rats and subcutaneously near the sacral region of another. The latter area was selected to determine if lepromata on the back were less prone to secondary infection than ventrally located lesions. A third group was inoculated intramuscularly as described above with the "Puerto Rican" strain. Six months after inoculation all of the rats in the above groups had well-developed lepromata, and clinically the two strains were indistinguishable at the time therapy was initiated.

The animals were examined three times weekly for clinical evidence of disease. Lepromatous lesions, if present, were measured by the same person with the aid of a plastic ruler. Autopsies were performed on all animals at the time of death or whenever an experiment was terminated. Films for acid-fast bacilli were prepared routinely from tissue at the site of inoculation, from the liver, spleen, and lung, as well as from any other tissue where macroscopic abnormalities were observed. Cultures for evidence of intercurrent infection were made from the heart's blood and occasionally from other sites, provided that the condition of the animal was suitable for bacteriologic examination when examined post mortem. Whenever doubt existed concerning any lesion observed grossly, histologic sections were prepared and examined microscopically.

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<sup>4</sup> Promin was supplied by Parke-Davis and Company, Detroit, Michigan.

<sup>5</sup> Diasone was furnished by the Abbott Laboratories, North Chicago, Illinois.

<sup>6</sup> Penicillin was provided by the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

<sup>7</sup> Streptomycin was made available by Merck and Company, Inc., Rahway, New Jersey, and by Squibb Institute for Medical Research, New Brunswick, New Jersey.

The course of the disease generally progressed in the following manner. After inoculation, the infected animal continued to gain weight and otherwise appeared normal for two to three months, at which time a palpable lepioma usually formed at the site of inoculation. As the local lesion became larger, the infection spread to other organs, particularly to the adjacent lymph nodes, the spleen, liver, and lungs. The hair became coarse, alopecia developed, and the animal became emaciated. Subsequently, extensive ulcerations occurred over the lepromatous masses. Not infrequently epicardial lesions developed. Death usually occurred within eight to fourteen months after inoculation. During the advanced stages of the disease the animals were prone to intercurrent infection and care was taken to isolate such animals immediately.

## RESULTS

### *Promin*

A dosage of approximately 50 mg of Promin administered daily as a component of the diet did not prevent the development of murine leprosy nor change the character of lesions typical of the disease. This dosage retarded the growth of the leproma at the site of inoculation, however, and delayed the progress of the disease, thereby increasing the survival time of treated rats. As soon as the infection became well established the pathogenesis of the experimental disease was not unlike that observed in untreated rats. Of 20 infected rats treated with Promin, one died of an intercurrent infection one week after the study was undertaken. A year later, 18 (95 per cent) of the remaining 19 rats still survived as compared with 15 (75 per cent) of a group of 20 untreated animals employed as controls. The physical condition of the treated rats was superior to that of the untreated controls, many of whom were moribund. Eighteen months after the experiment was undertaken only 2 (10 per cent) of the controls were living as compared with 9 (47 per cent) of the rats receiving Promin. In both groups of rats the disease was advanced, however, and because of their moribund state the animals were sacrificed (table 1).

### *Diasone*

A dosage of 0.5 Gm of Diasone per Kg of body weight injected subcutaneously daily for five months failed to suppress the development of lepromata. The course of the disease in the treated rats progressed like that of the untreated controls and 14 (93 per cent) of 15 treated rats had nodules from 0.5 cm to 2.0 cm in diameter at the time the drug was withdrawn. One of the rats had died as a result of an accident. Seven (70 per cent) of 10 untreated controls had similar lesions. Ten months after inoculation, 12 (80 per cent) of the rats receiving Diasone still survived. They were very ill, however, and 6 had large lepromatous ulcers at the site of inoculation. Seven (70 per cent) of the untreated rats were living, 2 of which had ulcerating nodules comparable to those present in the treated group. During the next month so many deaths occurred as a result of an intercurrent pulmonary infection the experiment was terminated (table 1).



*Penicillin*

Therapy with a single daily dose of 1,000 units of aqueous sodium penicillin for five months failed to influence the course of the disease and the treatment was discontinued. Seventeen (85 per cent) of 20 animals had lepromata from 0.5 cm to 2.0 cm in diameter. Fifteen (75 per cent) of 20 untreated controls had similar nodules. The experiment was terminated one year after treatment was initiated, at which time 12 (86 per cent) of 14 of the surviving rats had large lepromatous ulcers as compared with only 6 (40 per cent) of 15 untreated controls. As a matter of fact, the general physical condition of the surviving treated

TABLE 1

*Comparative Therapeutic Efficacy of Promin, Diasone, and Penicillin in Experimental Murine Leprosy*

DRUG	GROUP	NUMBER RATS	MONTHS AFTER INOCULATION	SURVIVALS	
				Number	Per cent
Promin	Treated*	19†	5	19	100
			12	18	95
			18	9	47
	Controls	20	5	20	100
			12	15	75
			18	2	10
Diasone	Treated‡	15	5	14	93
			10	12	80
			18	7	70
	Controls	10	5	9	90
			10	7	70
			18	5	100
Penicillin	Treated§	20	5	20	100
			12	14	70
			18	20	100
	Controls	20	5	20	100
			12	15	75
			18	15	75

\* Approximately 50 mg administered in the diet daily for duration of experiment

† 20 animals in original group, one died of an intercurrent infection one week after inoculation

‡ Administered 0.5 Gm per Kg body weight daily, subcutaneously for 5 months

§ Administered 1,000 units daily, subcutaneously for 5 months

rats was considerably worse than that of the untreated controls, all of whom showed marked evidence of disease (table 1)

*Streptomycin*

Streptomycin in the dosages employed did not retard the progress of advanced lesions of murine leprosy. The survival time of some of the treated animals exceeded that of the untreated rats by one to two months. The average survival time of 15 rats treated with a total dosage of 125,000  $\gamma$  per Kg of body weight was 9.7 months, of 15 treated with 250,000  $\gamma$  per Kg of body weight was 10.4 months, and of 18 treated with 500,000  $\gamma$  per Kg of body weight was 9.1 months.

The average survival time of 15 untreated controls was 9.0 months. The rats receiving 50,000  $\gamma$  of streptomycin per Kg of body weight per day survived on the average of 1.4 months longer than the controls. The rats treated daily for five days with 25,000 and 100,000  $\gamma$  of streptomycin per Kg of body weight showed little increase in longevity over the untreated control animals (table 2). No difference in the resistance of the two strains of murine leprosy to streptomycin was detected.

The group of 20 control rats injected with the heated inoculum remained normal throughout the 18 months' observation period, at which time they were sacrificed. Films prepared from tissue removed from the site of inoculation showed no acid-fast bacilli.

TABLE 2  
*Evaluation of Streptomycin in Advanced Murine Leprosy*

DAILY DOSAGE	TOTAL DOSAGE 5 DAYS	NUMBER RATS	AVERAGE MONTHS SURVIVAL
<i><math>\gamma</math> per Kg body weight</i>			
25,000	125,000	15	9.7
50,000	250,000	15	10.4
100,000	500,000	18	9.1
Untreated	Controls	15	9.0
Heated inoculum		15	18.0*

\* Sacrificed after 18 months

#### DISCUSSION

Evaluation of the therapeutic efficacy of drugs in leprosy is difficult because observation of the patient is required from the time therapy is initiated until death occurs. In murine leprosy the problem is still laborious because approximately one year is required to complete a single experiment. Nevertheless, data that may be valuable in solving the problems of Hansen's disease can be accumulated comparatively rapidly from studies of the experimental infection in rats. It is significant that the results obtained with Promin, Diasone, penicillin, and streptomycin in murine leprosy are not inconsistent with the information acquired to date on the treatment of leprosy in man. None of the four agents effected a cure, but Promin markedly suppressed the infection in rats. Furthermore, the general health of this group of animals during the course of the disease was superior to that of the untreated controls. In these preliminary studies, only a single dose of the drug was tested, except in the case of streptomycin. Although the amounts of the drugs employed were in the same range as those used in man, as yet only the effect of the minimal dosage has been observed. Furthermore, in our studies Promin was administered orally with the food, whereas it was injected intravenously for the treatment of human leprosy (8). Unfortunately, facilities and personnel were not available to test a series of dosage levels.

In animals with advanced lesions, streptomycin appeared to possess only minimal therapeutic value, even with dosages equivalent to 6,000,000  $\gamma$  per day for a man weighing 60 Kg. It was anticipated, however, that treatment for a five day period would probably be inadequate. More recent studies, which will be reported later, on the therapeutic efficacy of streptomycin in early murine leprosy, in which the treatment was initiated on the day of inoculation and carried out for several weeks, are likewise disappointing. These observations are in contrast to preliminary studies *in vitro* on the effect of streptomycin on *Mycobacterium leprae murium* in suspensions of lepromatous tissue. In these experiments

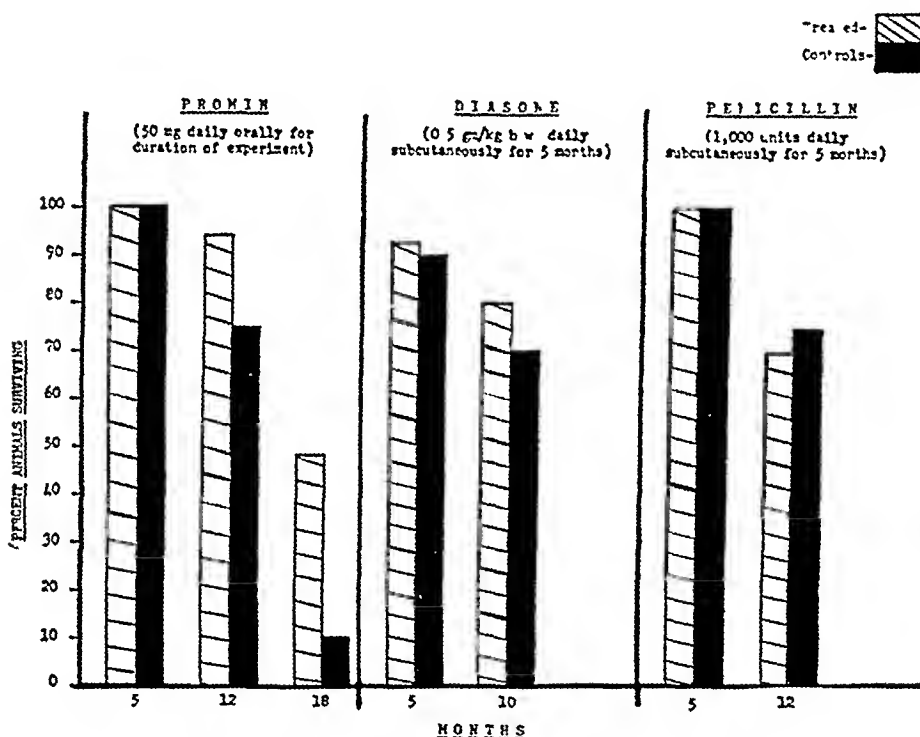


FIG 1 Comparative therapeutic efficacy of Promin, Diasone, and penicillin in experimental murine leprosy

the drug appeared to exert rather marked bacteriostatic and bactericidal action as determined by animal inoculation of the treated suspensions.

Therapy for five months with either Diasone or penicillin failed to alter significantly the course of the disease. Although treatment was not continued throughout the course of the disease, as was the case with Promin, it was obvious at the termination of therapy that no benefit was being derived from their use.

The above observations constitute only modest beginnings in this field and do not engender pessimism. Because of the slowly progressive character of murine leprosy, many months were required to become thoroughly familiar with the infection in order to develop a uniform experimental disease. With a rat colony now well established, much more rapid progress can be made.

## SUMMARY

1 The therapeutic efficacy of Promin, Diasone, and penicillin in early murine leprosy has been compared, employing dosages approximating those used in the treatment of leprosy in man. Streptomycin was evaluated in advanced murine leprosy only.

2 Approximately 50 mg of Promin, administered daily with the diet, suppressed the infection in rats and increased their longevity compared to that of untreated controls, but failed to effect a cure.

3 Streptomycin, employing daily dosages of 25,000, 50,000, and 100,000  $\gamma$  per Kg of body weight, administered subcutaneously every eight hours for five days, had minimal therapeutic effects on advanced murine leprosy.

4 Neither Diasone, 0.5 Gm per Kg of body weight, nor aqueous sodium penicillin, 1,000 units injected subcutaneously daily for five months, altered significantly the course of the disease.

## SUMARIO

*Quimioterapia de la Lepra Murina*

1 Empleando dosis aproximadas a las usadas en el tratamiento de la lepra en el hombre, comparóse la eficacia terapéutica de la promina, la diasona y la penicilina en la lepra murina temprana. La estreptomicina fué valorada solamente en la lepra murina avanzada.

2 Aproximadamente 50 mg de promina administrados a diario con el alimento suprimieron la infección en las ratas y acrecentaron su longevidad, comparada con la de los testigos no tratados, pero no efectuaron la curación.

3 La estreptomicina, empleada a dosis diarias de 25,000, 50,000 y 100,000  $\gamma$  por kg de peso y administrada subcutáneamente cada ocho horas durante cinco días, ejerció mínimo efecto terapéutico sobre la lepra murina avanzada.

4 Ni la diasona, 0.5 gm por kg de peso del animal, ni la penicilina sódica acuosa, 1,000 unidades, inyectadas subcutáneamente a diario durante cinco meses, alteraron en forma significativa la evolución del mal.

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# THE EVALUATION OF ANTITUBERCULOUS AGENTS WITH AVIAN TUBERCULOSIS IN CHICKS A COMPARISON OF DIHYDROSTREPTOMYCIN AND STREPTOMYCIN<sup>1</sup>

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## INTRODUCTION

The successful use of streptomycin as a therapeutic agent for certain forms of tuberculosis has resulted in efforts to develop additional and improved antituberculous agents and improved methods for *in vitro* and *in vivo* evaluation of such agents (1, 2). The guinea pig and the rabbit are highly susceptible to human and bovine types of *M. tuberculosis*, and consequently were the first animals used for studies on the efficacy of antituberculous agents. However, tests using these animals require 60 days for evaluation if acute infections are used, and 120 days if chronic infections are induced. A more rapid and economical test using mice and requiring only 28 days for completion has been introduced by Youmans (3,4). Martin (5) also recommends the mouse test.

Although it has been known that avian tuberculosis can be produced experimentally in the natural host (6), to our knowledge this infection has not hitherto been investigated as a method for the evaluation of antituberculous agents. Studies in this laboratory showed that a rapid and satisfactory infection could be produced in chicks by intravenous inoculation of avian type tubercle bacilli and that the infection responded to treatment with streptomycin. Furthermore, good correlation was observed between the level of drug dosage and response to treatment. The availability of dihydrostreptomycin offered an opportunity to apply the chick test to a comparative evaluation of streptomycin and dihydrostreptomycin.

Dihydrostreptomycin was first described by Peck, *et al.* (7) and shortly thereafter Youmans, quoted by Bartz, *et al.* (8), found that its *in vitro* antituberculous activity was the same as that of streptomycin. Freedlander and French (9) then reported that both drugs had equal *in vivo* activity against experimental tuberculosis in guinea pigs. On the other hand, Donovan and Rake (10) reported that dihydrostreptomycin showed significantly lower *in vitro* antituberculous activity than streptomycin, in a more recent publication (14), however, they report the two drugs to be equal in activity. One of us, in a recent report by Edison, *et al.* (11), summarized the results of a comparison of the efficacy of dihydrostreptomycin and streptomycin against avian tuberculosis, stating that these drugs were similar in antituberculous activity both by *in vitro* and *in vivo* tests. The present report is concerned with a description of the chick efficacy test and its application to the evaluation of streptomycin and dihydrostreptomycin.

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## MATERIALS AND METHODS

*M. tuberculosis*, human type, strain H37Rv and an avian type, strain Kirchberg, were used in these studies. The strains have been maintained by weekly serial passage in Dubos Tween-albumin medium. The drugs used were streptomycin calcium chloride complex (crystalline), 87.5 per cent pure\* and dihydrostreptomycin trihydrochloride (crystalline), 95 per cent pure†.

*Technique for in vitro Tests*

Tests were performed both with Dubos Tween-albumin medium (2) and with Youmans' modification of Proskauer and Beck's synthetic medium (1). One ml. amounts of aqueous drug solution sterilized by Seitz filtration were added to 9 ml. amounts of medium. The tubes were then inoculated with 0.1 ml. amounts of a 1:10 dilution of culture in Dubos medium adjusted with a Coleman 6A spectrophotometer to permit 90 per cent transmission of light at 620 mμ. The test cultures were observed for the presence of growth after 14 days of incubation at 37°C.

*Technique for in vivo Tests*

One-to-three weeks old male white leghorn chicks were used. The animals were fed a diet of Startena<sup>4</sup> ad libitum and were housed in an air-conditioned room at a temperature of 80°F. In each experiment, the chicks were divided into groups of 10 having comparable average weights. The animals were infected intravenously with 0.5 ml. amounts of 14 to 21 day old culture in Dubos medium adjusted with a Coleman 6A spectrophotometer to permit 60 to 63 per cent transmission of light at 620 mμ.

Treatment was by the intramuscular route and was given six days per week for a period of six or seven weeks. The drug solutions were prepared with distilled water to contain the desired daily dose per animal in 0.25 ml. of solution. The animals were weighed once weekly and the estimated weight gain for the next week was projected by analysis of the slope of the growth curve during the previous week. The drug dosage for the week was then calculated from the projected average weight. As subsequently determined from the observed weights, the error in dosage was rarely greater than 5 per cent, greater deviations occurred only when animals were in the terminal phase of infection.

The chicks surviving at the end of the test period as well as those dying during the course of the experiment were autopsied. The total body weights and the weights of the liver and the spleen were recorded. Pieces of liver, spleen, kidney, and lung were fixed in 10 per cent formalin. Histologic sections were stained with hematoxylin and eosin and, in the case of the liver, with an acid-fast stain.

To determine the extent and degree of the histopathologic changes, the following factors were analyzed:

I. *The number of tubercles per low power field*. 1 plus, indicating less than ten, 2 plus, ten to thirty, 3 plus, thirty to fifty, and 4 plus, over fifty.

II. *Amount of tissue replaced or displaced by the tubercles as observed per low power field*. 1 plus, equivalent to less than 10 per cent, 2 plus, 10 per cent to 33 per cent, 3 plus, 33 per cent to 50 per cent, and 4 plus, over 50 per cent.

III. *The developmental stage of the tubercles*. Preliminary studies confirmed Feldman's description of the pathogenesis of the miliary tubercle (7). The different stages in the development of the tubercle were arbitrarily divided. Not all the lesions in any one organ were at the same stage but they were sufficiently uniform to fall into one of the following stages:

1. Small collections of epithelioid cells are observed.

\* Purity estimated by rotation. These figures were obtained from Dr. T. J. Webb of The Research Laboratories of Merck & Co., Inc.

† Produced by Ralston-Purina Company, St. Louis, Missouri.

- 2 Tubercles are larger and composed of epithelioid cells and a thin rim of histiocytes, lymphocytes, and an occasional granulocyte
- 3 The epithelioid cells are fused and vacuolated
- 4 Necrotic changes are present within the tubercle
- 5 The centers of the tubercles are composed of necrotic epithelioid cells bordered by a layer of epithelioid syncytia and giant cells. The outer zone is composed of epithelioid cells, histiocytes, and a few fibroblasts and lymphocytes. Amyloid-like deposits may be present
- 6 At this stage the mature tubercle is found. It is composed of four zones: an inner necrotic zone, a zone of giant cells, a zone of epithelioid cells and histiocytes, and finally a zone of histiocytes, fibrous tissue elements, lymphocytes, and amyloid-like deposits

IV *Cellular reaction* The degree of cellular reaction was estimated by the number of layers that the lymphocytes and granulocytes formed about the average sized tubercle seen in the section. One cell layer was indicated by 1 plus, two cell layers by 2 plus, three cell layers by 3 plus, and four or more cell layers by 4 plus

TABLE 1

*Effect of Various Doses of Streptomycin on Mortality of Chicks Infected with M. tuberculosis Avian Type, Strain Kirchberg*

GROUP NUMBER	DOSE UNITS PER KG PER DAY	TREATMENT STARTED, WEEKS AFTER INJECTION	MORTALITY PER CENT
1	50,000	0	0
2	10,000	0	20
3	2,000	0	70
4	50,000	2	20
5	10,000	2	90
6	2,000	2	90
7	—	—	80
8	50,000	Not infected	0
9	10,000	Not infected	0
10	2,000	Not infected	0
11	—	Not infected	0

#### PROCEDURE AND RESULTS

The results of the *in vitro* tests showed that both drugs inhibited avian type, strain Kirchberg at a concentration of 5  $\gamma$  per ml and human type strain H37Rv at a concentration of 0.5  $\gamma$  per ml. The results were the same in Youmans' modification of Proskauer-Beck medium and in Dubos Tween-albumin medium.

The effect of graded doses of streptomycin was studied in experiment 1. The chicks were divided into groups treated as shown in table 1 and the experiment was terminated 50 days after infection.

The data on survival, presented in table 1, indicated that streptomycin was effective and that efficacy was directly correlated with level of drug dosage. Twenty per cent of the infected controls were alive at the end of the experiment. Among the groups treated immediately after infection, 100 per cent of the 50,000 unit group, 80 per cent of the 10,000 unit group, and 30 per cent of the 2,000 unit group were still alive. When treatment was delayed for 2 weeks, the survival rates

were respectively 80 per cent, 10 per cent, and 10 per cent for the 50,000, 10,000 and 2,000 unit groups

Inspection of growth curves, shown in figure 1, indicates that animals receiving 50,000 units per day beginning immediately after infection, as well as the uninfected controls treated with streptomycin, gained weight at the same rate as normal controls. With treatment at the 10,000 unit level begun immediately after infection and at the 50,000 unit level begun two weeks after infection (not included in figure 1), the rate of growth was depressed. Chicks in the

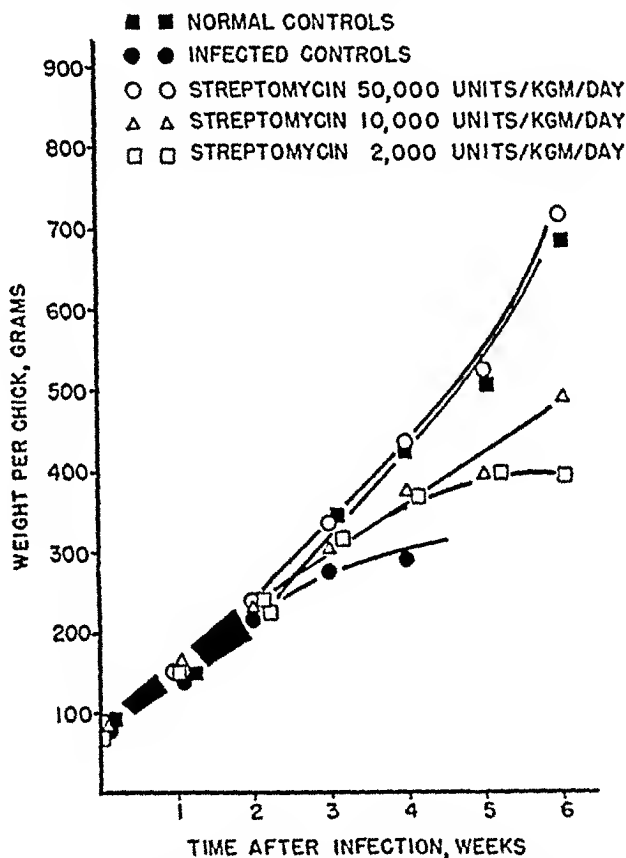


FIG 1 Growth curves of chicks infected with avian tuberculosis and treated with various doses of streptomycin

2,000 unit groups and in the 10,000 unit group given delayed treatment (not shown in figure 1) gained weight at a decreasing rate and at the sixth week their weights tended to remain stationary or to decline. The growth curves of the animals in these groups were above those of the infected controls.

The efficacy of dihydrostreptomycin as compared with streptomycin was studied in experiments 2 and 3. In experiment 2 the drugs were administered on an equal weight basis which did not compensate for differences in the estimated purity. The higher dose was established at 77 mg per Kg per day, this dose was equivalent to 50,000 units per Kg per day. In experiment 3 the drug dosage was



adjusted to compensate for the differences in estimated purity. The higher dose of streptomycin was again 77 mg per Kg per day and dihydrostreptomycin now 65.5 mg per Kg per day. The lower doses were again one-tenth those of the higher ones.

The comparative efficacy of the antituberculous agents in these experiments was evaluated by an analysis of growth curves, mortality data, and pathological changes in the liver. The growth curves for experiment 2 are shown in figure 2, those for experiment 3 were similar and are therefore not presented graphically.

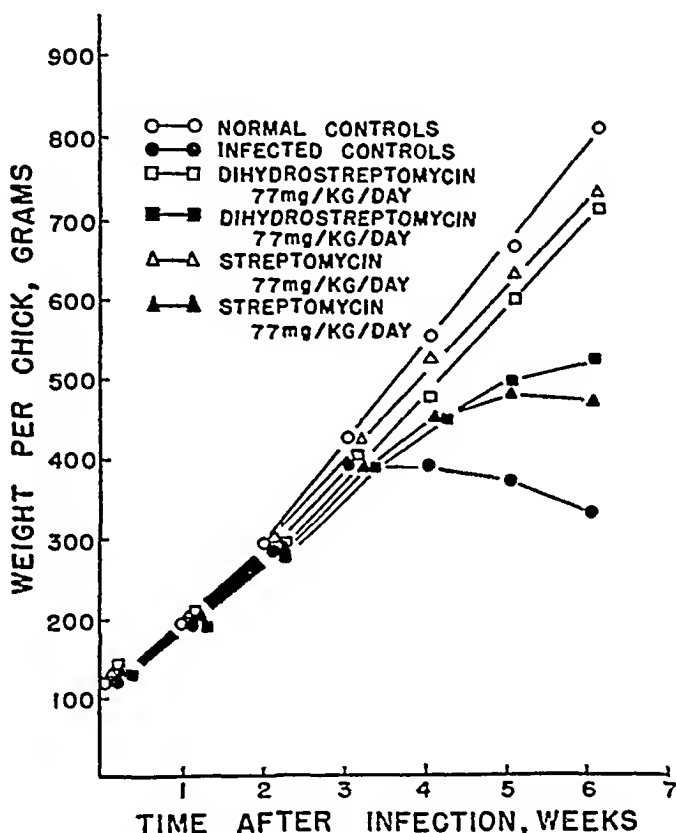


FIG 2 Growth curves of chicks infected with avian tuberculosis and treated with streptomycin or dihydrostreptomycin

The mortality data and data on the amount of liver tissue replaced by tubercles are given in table 2. The pathological findings for experiment 3 are further summarized in table 3.

In both comparative tests the infected control animals gained weight at a normal rate for the first 2 weeks and then showed a progressively decreasing rate of growth. Deaths occurred beginning with the third week. At the end of the sixth week 80 per cent of the controls were dead in experiment 2 and 90 per cent in experiment 3. Animals treated with the higher level of both drugs in both experi-

ments gained weight at a rate slightly below that of normal chicks and the drug control groups. There were no significant differences between the weight curves of the groups given the higher doses of either drug.

At the lower dosage level, differences were observed in the rate of mortality which could be correlated with the amount of drug administered. In experiment 2, where identical weights of drug were used, no deaths were observed among chicks treated with dihydrostreptomycin but 50 per cent of the chicks treated

TABLE 2

*Effect of Streptomycin and Dihydrostreptomycin on Mortality and Tissue Involvement of Chicks Infected with M. tuberculosis Avian Type, Strain Kirchberg*

GROUP	DRUG	DOSE MG PER KG		MORTALITY PER CENT	AMOUNT OF LIVER TISSUE REPLACED BY TUBERCLES AVERAGE OF GROUP
<i>Experiment 2</i>					
1	Streptomycin	77.0	Not infected	0	—
2	Streptomycin	77.0	Infected	0	1.7+
3	Streptomycin	7.7	Infected	50	3.1+
4	Dihydrostreptomycin	77.0	Not infected	0	—
5	Dihydrostreptomycin	77.0	Infected	0	1.5+
6	Dihydrostreptomycin	7.7	Infected	0	3.0+
7	None	—	Infected	80	4.0+
8	None	—	Not infected	0	—
<i>Experiment 3</i>					
1	Streptomycin	77.0	Not infected	0	—
2	Streptomycin	77.0	Infected	0	1.7+
3	Streptomycin	7.7	Infected	50	3.8+
4	Dihydrostreptomycin	65.5	Not infected	0	—
5	Dihydrostreptomycin	65.5	Infected	0	1.9+
6	Dihydrostreptomycin	6.6	Infected	40	3.1+
7	None	—	Infected	90	3.8+
8	None	—	Not infected	0	—

with streptomycin were dead at the end of the sixth week. In experiment 3, in which the amount of dihydrostreptomycin administered was lowered to compensate for the higher purity as compared with streptomycin, the mortality at the end of the sixth week for the dihydrostreptomycin treated group was 40 per cent as compared with 50 per cent for the group treated with streptomycin.

The growth curves for animals receiving the lower dose of drug were intermediate between those for groups receiving the higher dose of drug and the infected control group. The rate of growth at the lower drug dosage began to decline in the third week and decreased progressively thereafter. In experiment 2

the growth curves were closely similar until death ensued in the streptomycin-treated group, whereas in experiment 3 the dihydrostreptomycin-treated chicks gained weight more rapidly than those treated with streptomycin

TABLE 3

*Histopathological Changes in Livers of Treated and Untreated Chicks Infected with Avian Tuberculosis, Strain Kirchberg*  
Experiment 3

GROUP NUMBER	CHICK NUMBER	NUMBER OF TUBERCLES	AMOUNT OF TISSUE INVOLVED	AGE OF TUBERCLES	DEGREE OF CELLULAR REACTION	DIED OR SACRIFICED
I Infected not treated	228	4+	4+	4	0+	D
	229	1+	2+	3	4+	S
	230	4+	4+	4	0+	D
	231	4+	4+	4	0+	D
	232	4+	4+	4	0+	D
	233	4+	4+	3	1+	D
	234	4+	4+	4	1+	D
	235	4+	4+	4	0+	D
	236	4+	4+	4	0+	D
	237	4+	4+	4	0+	D
II Infected treated with streptomycin 77 mg per Kg	238	3+	2+	1	2+	S
	239	3+	2+	2	2+	S
	240	3+	2+	1	3+	S
	241	2+	2+	2	2+	S
	242	3+	2+	2	2+	S
	243	2+	1+	2	3+	S
	244	3+	2+	1	2+	S
	245	3+	2+	2	4+	S
	246	1+	1+	1	4+	S
	247	1+	1+	2	4+	S
IV Infected treated with dihydrostreptomycin 65.5 mg per Kg	258	2+	1+	1	3+	S
	259	3+	3+	3	3+	S
	260	2+	2+	1	1+	S
	261	2+	1+	2	3+	S
	262	1+	2+	1	4+	S
	263	2+	2+	1	2+	S
	264	3+	2+	2	2+	S
	265	2+	2+	1	2+	S
	266	2+	2+	1	4+	S
	267	2+	2+	1	4+	S

The histopathologic findings in both experiments were similar (table 3). The livers of the infected controls, most of which died before the test was terminated at 42 days, showed that more than 75 per cent of the tissue field was replaced by tubercles (4 plus lesion), the maximum amount of tissue reaction that could be expected at this stage of the disease. Little or no lymphocytic reaction was seen about the tubercles. The spleens revealed a similar histopathologic picture and

the weights of both livers and spleens of the infected controls were greater than in the drug-control or normal control birds. The lungs and kidneys presented only an occasional tubercle.

Both streptomycin and dihydrostreptomycin had a definite effect on the histopathologic picture. At the higher level of treatment with both drugs, the tubercles in the livers involved or displaced less tissue, were fewer, smaller, at an earlier stage, and were surrounded by a distinct coat of infiltrated cells, principally lymphocytes. The effect on the spleens paralleled that seen in the livers but was more variable. The weights of the livers and spleens of these treated animals averaged the same as normal uninfected birds, namely 5 per cent and 0.5 per cent, respectively, of the total body weight as compared with 15 per cent and 0.8 per cent of the total body weight in the infected controls. The increase in

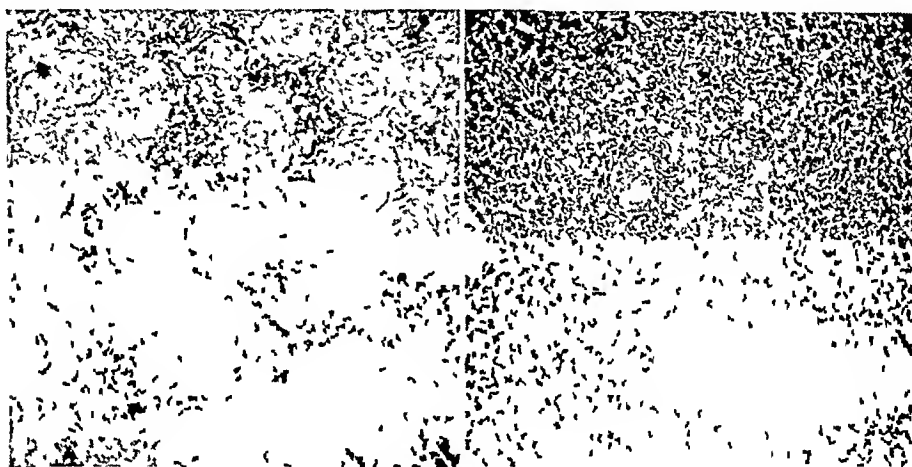


FIG 3A (Left) Liver of infected control chick, 6 weeks after infection

FIG 3B (Right) Liver of infected chick treated with 65.5 mg of dihydrostreptomycin per Kg per day, 6 weeks after infection

weights of the livers and spleens in infected birds, both treated and untreated, corresponded with the amount of tuberculous involvement.

In birds receiving one-tenth of the higher dose, the effect of both drugs was still quite noticeable. It will be recalled that at these levels the growth curves were above those for the infected controls, and a higher proportion of the treated animals as compared with infected controls were alive at the end of the test period. Microscopic examination of the livers, however, showed a degree of tuberculous involvement approaching that seen among infected controls. The extent of involvement in the spleen was less than that observed in the controls, but there was considerable variation in the reaction among individual treated animals.

Sections of liver stained by an acid-fast technique revealed that the number of acid-fast bacilli present in the tubercles was directly correlated with the degree of tuberculous involvement.

Photomicrographs of liver from an infected control chick and a treated chick

are shown in figure 3. Four small lesions may be seen in the section of the liver of the treated animal.

In addition to the three trials used in the present studies, seven other chick tests have been performed with the same infecting inoculum. In all but one of the 10 trials, 80 to 100 per cent of the infected controls were dead by the end of the seventh week. The rate of growth for chicks in all trials began to decline between the third and fourth weeks and decreased rapidly thereafter.

#### DISCUSSION

Avian tuberculosis is now used by our laboratory as one of the *in vivo* screening methods for antituberculous activity. This infection shows a number of desirable features. The test animal is a natural host for the disease, the host-parasite relationship shows a low degree of variability, and the relationship can be controlled readily. In addition, the chick is a desirable experimental animal because its genetic lines and nutritional requirements are well known and significant intercurrent infections are minimal at this age. There is also a low risk of laboratory infection because avian type rarely produces disease in man.

With the chick test, highly reproducible assessment of comparative efficacy may be expected. The results show that the factors studied to determine the degree of tuberculous involvement, namely, mortality rates, growth curves, microscopic changes, weights of liver and spleen, and the number of acid-fast bacilli present in the liver, were generally directly correlated with each other. We have observed a higher degree of variability for mortality rates and appearance of tuberculous lesions in mice infected with human type. As has been emphasized by other investigators, however, mortality by itself is not a highly reliable index of efficacy. The inhibition or regression of tuberculous lesions is the more reliable criterion.

In this regard, observations of both gross and microscopic changes may be used in assessing efficacy by mouse and guinea pig test methods. In the chick, the acute infection used in this study does not lead to the formation of gross lesions. Consequently, the pathological alterations in the tissues are determined by microscopic examination. The uniformity of the distribution of the lesions and their characteristic appearance simplify the evaluation of the pathological changes.

The growth curve in the chick test is a useful index of morbidity because the progressive decrease in the rate of growth of infected chicks as compared with the normal controls closely parallels the development of the tuberculous lesions. The rate of growth is also useful in the guinea pig test, but the growth of guinea pigs does not follow as precise and predictable a trend as is observed with chicks. In the mouse test, a significant decline in animal weight occurs only in the terminal phase of infection.

The chick test, however, does not completely replace *in vivo* tests with human type in guinea pigs or mice, since the agents to be tested may not possess the same degree of activity against both human and avian type. This difference, as

determined by *in vitro* tests, should indicate the degree of reliance that may be placed upon the chick, test

Our *in vitro* studies, showing that *M. tuberculosis* human type is equally sensitive to streptomycin and dihydrostreptomycin, are in agreement with the findings of Youmans and Karlson (12) and Feldman, *et al* (13). Similarly the avian type is equally sensitive to both drugs. However, avian type is more resistant than human type to the action of both drugs.

Although the avian type was more resistant than human type to the action of streptomycin and dihydrostreptomycin *in vitro* and the test chicks were given a massive infecting inoculum, the infection was relatively sensitive to the action of both drugs. Reports by other investigators indicate that, with mice, doses of streptomycin in the range of 20,000 to 100,000 units per kg per day and, with guinea pigs, 15,000 units per Kg per day are adequate to produce a good therapeutic response. In the chick a dose of 10,000 units per Kg per day produced a detectable therapeutic effect and 50,000 units were required to produce a marked effect. The chick thus compares favorably with the guinea pig or mouse when considering sensitivity of response to streptomycin or dihydrostreptomycin. The dosage range of 10,000 to 50,000 units per Kg per day corresponds roughly to a range of 0.5 to 3 Gm per day for man.

Our *in vivo* studies showing that dihydrostreptomycin is as active as streptomycin are in agreement with the findings of Freedlander and French (9) and Feldman, Karlson and Hinshaw (13) using human type in the guinea pig, and Rake, *et al* (14) using bovine type in the mouse.

The data in this report do not indicate the effect of treatment on a well-established tuberculous process.

#### SUMMARY

1 A new *in vivo* test for assessment of antituberculous activity is described which employs intravenous inoculation of chicks with avian type of *M. tuberculosis*. This test gives highly reproducible results. The effect of treatment is evaluated on the basis of growth curves, mortality data, and histopathologic changes in the liver. The last includes the number of tubercles, the amount of tissue displaced or replaced by the tubercles, the age of the tubercles, and the degree of lymphocytic and granulocytic reaction.

2 The method is applicable to substances showing comparable *in vitro* activity against human and avian types.

3 This test, applied to a comparison of the efficacy of dihydrostreptomycin and streptomycin, indicates that these drugs are of comparable efficacy against avian tuberculosis in the chick.

#### SUMARIO

*Valuación de los Agentes Antituberculosos con la Tuberculosis Aviar de los Pollos. Comparación de la Dihidroestreptomicina y la Estreptomicina.*

1 El nuevo ensayo *in vivo* aquí descrito para la valoración de la actividad antituberculosa utiliza la inoculación intravenosa de los pollos con el tipo aviario

del *M tuberculosis* Este ensayo da resultados muy reproducibles El efecto del tratamiento se valúa a base de las curvas del desarrollo, los datos de mortalidad y las alteraciones histopatológicas en el hígado, comprendiendo estas últimas número de tubérculos, proporción de tejido desplazado o suplantado por los tubérculos, edad de los tubérculos e intensidad de la reacción linfocitaria y granulocitaria

2 El método tiene aplicación a sustancias que revelen actividad *in vitro* comparable contra los tipos humano y aviario

3 Este ensayo, aplicado a una comparación de la eficacia de la dihidroestreptomycin y la estreptomycin, indica que estas drogas poseen eficacia comparable contra la tuberculosis aviaria en el pollo

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# ROUTINE CHEST PHOTO-ROENTGENOGRAPHY IN BARONESS ERLANGER HOSPITAL, CHATTANOOGA, TENNESSEE

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## INTRODUCTION

Since 1930, there have been occasional references in the literature to articles evaluating routine chest roentgenography of individuals admitted to general hospitals. Perhaps the most outstanding of these articles was that of Plunkett and Mikol in 1940 (1). These writers reviewed preceding articles by others and, in addition, reported the results of a study of routine chest roentgenograms in nearly five thousand persons admitted to fourteen general hospitals. They stated

Because of the existence of tuberculosis in some of the patients who are admitted to general hospitals for other conditions, they constitute a population group of considerable importance in the epidemiology of tuberculosis. While to the individual patient early diagnosis is important, the significance of this to the hospital personnel, the family and the community deserves emphasis. Although x-ray films will discover these cases, nevertheless, the x-ray has not been as commonly used as the need would indicate for the diagnosis of not only tuberculosis but also other diseases of the chest.

The State Department of Public Health, acknowledging such a need in Tennessee, offered to Baroness Erlanger Hospital in Chattanooga the permanent loan of 70 mm. photo-roentgen equipment for the purpose of doing chest roentgenograms routinely on all persons admitted to the hospital. This offer was accepted early in 1946 and the unit was delivered in March of the following year. Previously there had been put into use by the Chattanooga-Hamilton County Health Department a stationary photo-fluorograph for clinic use, and a mobile unit for mass roentgenographic examination of persons in industry, schools, and communities. The equipment was placed at the general hospital, therefore, to round out the case-finding program and to make available to another population group routine chest roentgenograms for the discovery of cases of tuberculosis.

A brief comparison of the amount of tuberculosis found by the three photo-roentgen survey units now operating in Chattanooga is the purpose of this paper.

## METHOD OF PROCEDURE

The stationary 35 mm. photo-fluorograph in the Health Department clinic has been used since June 1944 to examine foodhandlers, contacts, teachers, barbers, and beauty operators, persons applying for employment in certain industries (pre-employment), patients referred by physicians, persons desiring roentgenograms because of symptoms or for some other reason, a few students referred from schools, and a miscellaneous group designated as "other." Hereafter, the individuals included in this survey will be described as the "Clinic Group."

The mobile unit, a 70 mm. photo-fluorograph installed therein, has been in use since

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<sup>1</sup> Chattanooga-Hamilton County Health Department



March 1946. The population groups surveyed by this unit have been classified as community, industrial, and school. The classifications are for the most part self-explanatory. The community group includes persons in the various sections of Chattanooga and Hamilton County who are adults living in residential areas. The industrial group in Hamilton County consists primarily of workers employed in textile plants, foundries, and metal factories, and in various small metal, wood, and machine shops or factories. The school group is made up of students 15 years of age or over. The term "mobile unit" will be used to refer to this whole group.

In Barone's Hospital it was planned to obtain chest roentgenograms routinely on all persons admitted to the hospital, but this was not attempted during the first year. Included in the survey group are employees and service patients (any nonpaying patients, primarily indigent), and also a few private patients and persons referred from the emergency room. The term "hospital group" will be used in referring to this group of persons.

Analyses of the results of all three surveys were not made during the same year but the results are, nevertheless, readily comparable. Analyses of the clinic and mobile unit groups are for the year 1946, and analysis of the hospital group is for the period April 1 through December 31, 1947. An early report of this sort seems indicated because of the relatively high percentage of pulmonary tuberculosis discovered during the first year in the group of persons who were routinely examined roentgenographically on admission to the hospital.

TABLE 1  
*Results of Photo roentgen Examinations from Three Types of Surveys*  
*Chattanooga Hamilton County*  
1946-1947

GROUP	NUMBER EXAMINED	CASES	
		NUMBER	PERCENT
Health department clinic, 1946	13,966	383	2.7
Mobile unit, 1946	14,293	290	2.0
Hospital unit, 1947	5,187	193	3.7
All surveys	33,446	866	2.6

#### SURVEY FINDINGS

Thus far approximately 113,500 examinations were made with the photo-fluorographic units in a community with a population of 193,591<sup>2</sup>. In 1946, as may be seen in table 1, there were 13,966 first examinations at the clinic, 14,293 first examinations at the mobile unit, and in 1947 there were 5,187 first examinations at the hospital. The number of cases of tuberculosis discovered as a result of first examinations in the combined surveys and in different types of surveys may be seen in table 1.

In the three types of surveys combined, 33,446 patients received chest roentgenograms for the first time. Of this group, 866 persons, or 2.6 per cent, were found to have definite tuberculosis (table 1). In contrast to this average rate for the whole group, the percentage of persons found to have tuberculosis on examination at the mobile unit was 2.0, while in the Health Department clinic the percentage was 2.7. In the hospital group the relatively high percentage of 3.7 persons with tuberculosis was discovered.

<sup>2</sup> Estimated population in 1946, Tennessee Department of Health

The efficiency of the three types of surveys in finding cases of tuberculosis in the population may also be seen in table 1. Three and seven-tenths per cent of the hospital group were discovered to have tuberculosis in contrast to 2.7 of the Health Department clinic group and 2.0 of the mobile unit group.

#### DISCUSSION

Although the highest percentage of cases of tuberculosis (3.7) was found in the hospital group, the finding of 2.0 and 2.7 per cent of persons examined with tuberculosis in mobile unit and clinic groups should not be minimized. Such surveys have proved their value during recent years and there are many references in the literature concerning the success of mass roentgenographic studies. Nevertheless references to articles setting forth the value of routine roentgenographic examination of hospital admissions are rather few and far between. Such articles as are found stress the risk to the medical student, nurse, or hospital employee of cases of unrecognized tuberculosis in the hospital population, but few dwell at any length on the exceptional opportunity for tuberculosis case finding provided by the hospital population. Moreover, references to the responsibility of general hospitals in the case-finding program are strikingly absent from the literature. It would seem that the finding of a high percentage of cases of unrecognized tuberculosis among hospital employees and patients imposes a responsibility that is difficult to ignore.

It is of interest to consider briefly the makeup of the hospital survey group as compared to the Health Department clinic group. The mobile unit population composition is obvious from the titles of the previously mentioned subgroups (industry, community, school). In none of these subgroups has the finding of tuberculosis been higher than 2.7 per cent. There is no outpatient tuberculosis clinic in connection with Baroness Eilanger Hospital, and patients are admitted for hospital and clinic services for any of the many reasons for which general hospitals admit and care for patients. Outside of the fact that the patient enters the hospital or outpatient department for some complaint other than tuberculosis, and except for diabetic, tumor and venereal disease clinics (which might be expected to have considerable unrecognized tuberculosis), there is no special subgroup that contributes to the high percentage (3.7) of persons found in the hospital population with tuberculosis. On the other hand, in the clinic were examined such subgroups as contacts (5.5 per cent with tuberculosis), barbers and beauty operators (7.7 per cent), and patients referred by physicians (9.3 per cent), in all of whom cases of tuberculosis were discovered relatively frequently. This makes it all the more apparent that routine chest roentgenographic examinations of patients admitted to general hospitals should be seriously considered as a responsibility of the hospital and as its contribution to the community tuberculosis control program.

The success of any tuberculosis case-finding program depends upon the finding of early cases of the disease. In the clinic and mobile unit groups it was not unusual to find that 65 to 70 per cent of the lesions discovered were minimal in extent. For this reason it was quite surprising to learn that among the hospital

population examined 92 per cent of the lesions were minimal in extent. In only 7 per cent of the patients were the lesions moderately advanced and in only one per cent were the lesions far advanced. Minimal active lesions comprised 21 per cent of the total number of cases of tuberculosis discovered. The amount of tuberculosis found among young adults was also quite high in the hospital group.

With the advent of photo-fluorography it was expected that many general hospitals would take advantage of this economical technique and adopt chest roentgenograms as a routine procedure. This did not occur. As late as 1945, Hilleboe and Morgan (6) reviewed the work of investigators in Ann Arbor, New York, and Chicago where from 1.5 to 2.8 per cent of persons admitted to general hospitals were found to have reinfection type tuberculosis. They concluded that the value of mass radiographic methods in the examination of persons admitted to general hospitals was evident. Furthermore, they hoped that soon all general hospitals would provide routine roentgenographic examinations of the chest as they were already providing routine serologic tests for syphilis.

Plunkett and Mikol, in reviewing the studies of Mills and Stewart (2), Hodges (3), and of Pohle, Paul and Oatway (4) pointed out that these various authors had discovered significant reinfection type tuberculosis in 0.3 per cent to 1.4 per cent of persons who had routine chest roentgenograms on admission to a hospital. The cases discovered were not detected clinically, were unsuspected, and were admitted to the hospitals for reasons other than tuberculosis. They would have remained undiscovered cases of the disease during their hospital residence if a roentgenographic examination had not been made. Each of the three studies reviewed included children, and the surveys were also conducted in hospitals in the Midwest where tuberculosis morbidity and mortality are relatively low.

In their own study in upstate New York, Plunkett and Mikol (1) reported the results of 4,853 routine chest roentgenograms of persons over 15 years of age admitted to general hospitals. As a result of the roentgenographic examinations, 128 patients or 2.6 per cent were found to have reinfection type tuberculosis. In the whole group, 51 individuals, or 1.1 per cent, had significant lesions. In contrast, the relatively similar group of 5,187 persons examined at Erlanger Hospital in the same type of program, yielded 193 patients, or 3.7 per cent, with reinfection type tuberculosis. Moreover, of those found to have tuberculous lesions, 21 per cent were considered to have minimal active pulmonary tuberculosis. It is estimated that of the whole group examined between 1.3 and 1.5 per cent will prove to have clinically significant lesions after more prolonged study. Plunkett and Mikol pointed out the magnitude of the tuberculosis problem in general hospitals. They also stated in part, "In view of the unquestioned value of the x-ray its comparatively low average utilization for chest conditions is regrettable."

Chadwick and Pope (5) in 1942 confirmed the serious risk to student nurses and medical students of unrecognized cases of tuberculosis in hospitals, but they stated further, "General hospitals, also offer a fertile field for case finding. Obviously routine x-ray of all general hospital admissions would do much to uncover unrecognized tuberculosis in the community."

These various authors have clearly emphasized the value of tuberculosis case finding in general hospitals. To date, however, mass radiographic procedures are taken for granted in population groups of other kinds, but there still seems to be some reluctance to use routine chest roentgenography in general hospital populations. Since this particular population group is available without any preliminary work-up like that necessary with all other types of surveys, this reluctance is somewhat difficult to understand. Though it undoubtedly would be of value there is little need, as far as case finding alone is concerned, for the preliminary educational build-up, for the intensive survey campaign and all its contacting and publicity. In fact it appears to the writer that this one population group has been handed to the case finder "on a silver platter."

#### SUMMARY

The results of clinic, mobile unit, and hospital photo-fluorographic surveys in Hamilton County, Tennessee, have been presented. Data from these surveys have been presented in this early report because of the obvious need for information relative to the value of hospital surveys. Other hospital survey studies have included children, have been made up of a rather small number of adults admitted to hospitals over a short period of time, and have been carried on in areas with low tuberculosis morbidity and mortality rates. The reverse is true in the case of the present study in which significant tuberculous lesions were detected in 37 per cent of the persons routinely examined roentgenographically on admission to the hospital.

#### CONCLUSIONS

1 Insufficient attention has been paid to date to studies showing the value of obtaining routine chest roentgenograms of persons admitted to general hospitals.

2 Comparison of Health Department clinic, mobile unit, and hospital photo-roentgen surveys reveals that the hospital survey finds the highest percentage of cases of reinfection type of tuberculosis.

3 Data from Baroness Erlanger Hospital, Chattanooga, Tennessee, show that 37 per cent of persons admitted and routinely examined roentgenographically had unrecognized reinfection type tuberculosis. Between 13 and 15 per cent of the hospital group routinely examined are believed to have clinically significant tuberculous lesions.

4 The responsibility of the modern general hospital in the tuberculosis case-finding program in the community cannot be over-emphasized in the light of modern case finding techniques.

#### CONCLUSIONES

*La Roentgenofotografía Torácica Sistemática en el Hospital Baroness Erlanger*

1 Hasta la fecha se ha prestado insuficiente atención a los estudios que revelan el valor de la obtención de radiografías torácicas sistemáticamente en las personas admitidas a los hospitales generales.

2 La comparación de las encuestas roentgenofotográficas en la clínica del departamento de sanidad, la unidad movable y el hospital revela que el último es el que descubre el mayor porcentaje de casos de tuberculosis tipo reinfección

3 Los datos del Hospital Baroness Erlanger, de Chattanooga, Tennessee, muestran que 37 por ciento de los enfermos recibidos y radiografiados sistemáticamente tenían tuberculosis tipo reinfección no reconocida. Opínase que de 13 a 15 por ciento del grupo hospitalario examinado sistemáticamente tienen lesiones tuberculosas de importancia clínica

4 A la luz de las modernas técnicas para descubrimiento de casos, no cabe exagerar la obligación que corresponde al hospital general contemporáneo en las obras de descubrimiento de casos de tuberculosis en la colectividad

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## EDITORIAL

### The Necessity for Accurate Evaluation of the Results of Thoracoplasty

Pulmonary resection in the treatment of tuberculosis has become a safer and more widely used procedure than it was a few years ago. The indications for and results of resection are still not clearly defined.

Since the choice of surgical procedures often lies between primary pulmonary resection and thoracoplasty, the need for more accurate and detailed reports of the results of thoracoplasty is becoming increasingly apparent. These reports should be subdivided so as to include an evaluation of the results of thoracoplasty according to the type of disease treated. The age, extent and location of the lesions, the size and type of cavities, and the presence of gross or suspected bronchial lesions are among the factors which undoubtedly influence the results of thoracoplasty to a considerable extent.

Too many published reports of the results of thoracoplasty in the past have failed to take these factors into consideration and have stressed only mortality statistics and the percentage of sputum conversions. A report of the results of thoracoplasty without taking these factors into consideration is analogous to reporting on the results of pneumonectomy without specifying whether the pneumonectomies were performed for carcinoma, for so-called bronchial adenoma, or for pulmonary suppuration.

It is hoped that many more reports on the results of thoracoplasty similar to that of Rubin and Klopstock, which appears in this issue of the Review, will be published in the near future and that authors will classify their cases according to clinico-pathologic groups so that comparison of results from various centers may be possible.

Too often our decision as to the type of surgical procedure to be employed in the treatment of pulmonary tuberculosis is based on impressions of results obtained in cases we have treated recently rather than on a statistical analysis of cases treated over a period of years. For this reason, it is important that those of us who are making such decisions review our thoracoplasty results and classify them according to the type of disease. Although we may not necessarily publish our findings, by making such analyses we will help to clarify the indications for thoracoplasty and primary pulmonary resection in our own minds. Another reason for making our own analyses is that there are bound to be discrepancies between reports of results of thoracoplasty from different centers because of individual variations in the interpretation of roentgenograms, variations in surgical techniques, and differences in the type of patients treated from racial and economic standpoints.

If the results of thoracoplasty can be proved to be poor in a certain type of disease, a trial of pulmonary resection certainly seems justified in that type. On the other hand, if the long term results of thoracoplasty in another type appear highly satisfactory, the use of primary pulmonary resection as an alternative procedure hardly appears justified until more is known concerning the late results of resection.

JOHN D. STEFLE

## LETTERS TO THE EDITORS

### THE EFFECT OF AMMONIUM IONS AND ALIPHATIC AMINES ON THE ABILITY OF VIRULENT MYCOBACTERIA TO BIND NEUTRAL RED

*To the Editors of the American Review of Tuberculosis*

It has been shown in an earlier report from this laboratory (Dubos, R J, and Middlebrook, G, *Am Rev Tuberc*, 1948, 58, 698) that virulent mycobacteria are capable of binding the basic dye neutral red in the form of its salt even under extremely alkaline conditions. Further analysis of this phenomenon has revealed that binding of the dye can be inhibited by certain surface active agents and cationic substances.

Cultures grown in the presence of high concentrations of asparagine (0.5 per cent) fail to bind neutral red unless they have been washed thoroughly—with 50 per cent methanol, for example—prior to the test. On the contrary, cultures grown in media free of amide and in which asparagine has been replaced by glutamic acid, give a positive neutral red test even without prior washing. We have established, on the other hand, that asparagine exerts its inhibitory effect only if added to the living microorganisms, whereas it fails to interfere with the binding of the dye if added to cell suspensions killed with 2 per cent phenol. These findings suggested that inhibition of binding of neutral red is brought about not by asparagine itself, but rather by some metabolic product of the virulent tubercle bacilli growing in the presence of the amide asparagine.

We have now established that ammonium salts (sulfate or chloride) and a number of aliphatic amines prevent virulent mycobacteria from binding neutral red at alkaline reactions, even when they are used in amounts as small as 1 cc of 0.001 M solution per mg of bacterial cells (dry weight). This inhibitory effect exhibits a marked degree of specificity as many other basic substances (aromatic amines, basic peptides and proteins, inorganic cations) have been found to be without effect on the binding of the dye. Among the substances tested so far, atabrine is one of the few possessing some activity in this respect.

Virulent mycobacteria treated with ammonium salts or with the lower aliphatic amines (methylamine hydrochloride, for example) recover the ability to bind the dye after they have been adequately washed, indicating that they combine reversibly with these substances. On the contrary, mycobacteria which have been treated with long chain fatty amines (tetradecylamine, octadecylamine) remain unable to bind the dye even after prolonged washing. It appears likely, therefore, that these long chain compounds become firmly bound to the bacterial bodies by virtue of their lipophilic properties.

Experiments carried out by Dr Samuel P. Martin and Cynthia H. Pierce, to be published later, have revealed that the ability of virulent mycobacteria to inhibit the migration of polymorphonuclear leukocytes (Allgower, M, and Bloch, H, *Am Rev Tuberc*, 1949, 59, 562) is neutralized when aliphatic amines are added to the system in concentrations sufficient to neutralize the ability of the microorganisms to bind neutral red.

RENÉ J. DUBOS  
EMMANUEL SUTER

THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH  
NEW YORK, N Y  
JUNE 27, 1949

## TOXIC EFFECTS OF DL SERINE ON VIRULENT HUMAN TUBERCLE BACILLI

*To the Editors of the American Review of Tuberculosis*

While studying the effect of amino acids on the growth of mycobacteria and on their ability to bind neutral red under alkaline conditions (Dubos, R. J., and Middlebrook, G., *Am. Rev. Tuberc.*, 1948, 58, 698) we have observed that dl serine, and to a less extent dl alanine, exert a marked toxic effect (bacteriostatic and bactericidal) on virulent human tubercle bacilli.

The toxicity of these amino acids can be readily demonstrated in a variety of synthetic and semi-synthetic culture media. We have studied its manifestations particularly in a medium consisting of mineral salts, glutamic acid (0.2 per cent), and serum albumin (0.5 per cent). Addition to the medium of the dispersing agent Tween 80 (0.02 per cent) facilitates observation of the results without affecting the outcome of the experiments. The culture media were inoculated with approximately  $10^8$  living bacilli (from a culture in Tween-albumin medium) per cc of medium.

Different cultures of mycobacteria vary appreciably in their susceptibility to the toxic effect of dl serine. The most resistant of those tested were three variants of human bacilli, which have become avirulent and have lost also the ability to bind neutral red in alkaline media (H37Ra, H4Ra and JH16Ra). These cultures could grow normally in concentrations of dl serine as high as 0.1 per cent. By contrast three fully virulent strains of human tubercle bacilli were inhibited by adding 0.01 to 0.02 per cent of this amino acid to the same medium.

Surprisingly enough, the bactericidal effect of dl serine can be recognized even at concentrations lower than those required for inhibition of growth. Thus, when the amino acid is added in amounts too small to inhibit bacterial multiplication (0.003 per cent for example), growth at first appears normal both qualitatively (as determined by the morphological appearance and staining characteristics of the bacilli) and quantitatively (as measured by turbidity of the culture). Within a few days, however, autolytic changes become manifest (loss of acid fastness and decrease in opacity) and subcultures in new media free of serine reveal that a large percentage of the bacilli fail to grow even after prolonged incubation. It is of interest that, simultaneously with this sterilizing effect of dl serine on growing cultures of virulent human tubercle bacilli, other cellular alterations take place which bring about a loss of ability of the microorganisms to bind neutral red in an alkaline environment.

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## THE INTRAVENOUS ADMINISTRATION OF P-AMINOSALICYLIC ACID<sup>1</sup>

*To the Editors of the American Review of Tuberculosis*

A serious objection to p-aminosalicylic acid as a chemotherapeutic agent for tuberculosis is the nausea and vomiting patients experience when the drug is administered by

<sup>1</sup> This study was supported by a grant from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service.



mouth. There is a wide variation in the amount of the drug which each individual patient can tolerate. Some complain only of anorexia on a daily dose of 10 to 15 Gm., others have severe nausea and vomiting on as little as 5 or 6 Gm.

In view of the fact that parenterally administered PAS in two subcutaneous doses per day produced favorable results on the course of tuberculosis in experimental animals, it was decided to explore the feasibility of the parenteral administration of the drug to patients.

An isotonic solution of sodium p-aminosalicylic acid adjusted to a pH of 7.35 is not irritating to tissues and can be given either subcutaneously or intravenously without discomfort. To prepare such a solution, suspend 22 Gm. (144 milli equivalents) of powdered PAS in approximately 100 cc. of pyrogen-free water. Dissolve 7.6 Gm. of sodium carbonate in 100 cc. of pyrogen-free water and add it slowly and with constant stirring to the PAS suspension. Using a glass electrode pH meter, adjust the final pH of the solution to 7.35 by adding, drop by drop, additional sodium carbonate solution, and then sterilize by passing through a Seitz filter. Dilute the filtrate to 1,000 cc. with sterile pyrogen-free water to obtain a clear amber solution. This preparation, if kept in a refrigerator, keeps for many weeks without deterioration.

Patients have received 500 cc. of this solution intravenously daily for up to six weeks without complaining and without sclerosis of the veins. More recently, intravenous solutions containing 33 Gm. of PAS per liter have been given without ill effects. If the solution is given too quickly and blood levels of more than 40 mg. per 100 cc. are produced, then the patient does become nauseated.

Liver function studies carried out before as well as after a course of intravenous PAS therapy did not show any evidence of liver damage in the small number of patients so far treated in this manner. Prothrombin times had a tendency to drop, but none went below 70 per cent of normal.

It remains to be seen if this has an influence on promoting pulmonary hemorrhage.

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## Strachimer A. Petroff

1883-1948

The late Strachimer A. Petroff was the last of the brilliant group of research men who were associated with Dr. E. L. Trudeau after his founding of the Trudeau Sanatorium, and who made up the famous "Trudeau Group." Lawrason Brown, E. R. Baldwin, Leroy U. Gardner, Fred Heise, Homer Sampson, and S. A. Petroff were all men who grew up around Dr. E. L. Trudeau and who made the name of Trudeau famous in the world of tuberculosis in the first third of the century when the solid ground-work of the struggle against tuberculosis was being laid.

Doctor Petroff was born in Varna, Bulgaria, in 1883 and studied at the University of Sofia. In 1900 he came to the United States as part of a "grand tour" of the world to complete his education. An early evidence of his independence of thought, which was later so fruitful to science, was a long-range political argument with his family. This resulted in cutting off all ties and leaving himself stranded in a foreign land with practically no knowledge of English and no means of support. Fortunately, as it turned out, he then "broke down" with tuberculosis and came to Trudeau Sanatorium. Here he attracted the attention of Doctors Lawrason Brown and E. L. Trudeau, who put him to work in the Research Laboratory and in 1907 put him on the Research Staff. In 1912 he married Mary Fears Gilmer, a nurse who was a fellow patient at Trudeau. This was an important turning point in his career. Her devotion to him and to his work proved to be of inestimable value to him, and their long and happy marriage contributed largely to his success. In 1921 he succeeded Dr. E. R. Baldwin as Director of the Research Laboratory at Trudeau Sanatorium where he remained until 1936. In 1937 he accepted the Directorship of the Bacteriological Laboratory at Sea View Hospital, Staten Island, N. Y., the largest tuberculosis hospital in the country, where the wealth of material available gave ample scope to his tremendous capabilities. This post he held until his retirement because of ill health to his home in Greenville, South Carolina, in 1946.

Doctor Petroff's contributions to science, and more particularly to tuberculosis, are listed in the more than one hundred articles that he published during his nearly forty years of active research work. He was a mechanical genius. Various pieces of laboratory apparatus—needles, slide holders, media, et cetera, are a few of the things he developed. In 1927 as co-author with Doctors Baldwin and Gardner he published *Tuberculosis—Bacteriology, Pathology and Laboratory Diagnosis*, a most valuable contribution.

His work on the dissociation of the tubercle bacillus had an important and far-reaching effect. It is difficult today to recall the enormous excitement in the world of tuberculosis workers elicited by the Lubeck disaster and the subsequent trial and world discussion of BCG. Doctor Petroff, because of his outstanding work in dissociation of the tubercle bacillus and of BCG was called by the

German authorities to testify in the Lubeck trial and his testimony against BCG is still debated

Doctor Petroff was widely honored during his lifetime. In 1923 he received a Doctorate of Philosophy from Columbia University where he had studied under the late Dr. Hans Zinnser. He received an honorary Doctorate of Science from Colgate University in 1932. He was an active member of the American Society of Bacteriologists, the Society of Experimental Biology and Medicine, the Society of Immunologists, and the American Editors and Authors Association.

He was a member of the National Medical Advisory Board in the First World War, and in 1928 a Special Member of the International Board of Health of the League of Nations. From 1931 to 1933 he was a member of the National Research Council.

In paying honor to Doctor Petroff at his passing, we not only honor a brilliant scientist but again pay tribute to that group of great men of which he was a part and to whom we in tuberculosis owe so much, the "Trudeau Group."

HENRY W. LEETCH

## George Chambers Anglin

1890-1948

Following a full day's medical duties on Tuesday, April 16, 1948, Doctor Anglin suffered an almost immediately fatal heart seizure during that night.

Born in Ireland, Doctor Anglin came to Canada in 1907, and was graduated from the University of Toronto in 1914. He served in the R. A. M. C. from 1915 to 1918. He continued as Director of the Chest Clinic at Christie Street Military Hospital, and during the Second World War was Chest Consultant for the three services in the Toronto Military District. For his services in the same capacity to the Norwegian Air Force he was signally honored by the King of Norway.

He was a member of the Staff of the Toronto Hospital and enjoyed a large consulting practice in allergic and chest diseases, with perhaps his deepest interest in tuberculosis. He had long been a member of the Trudeau Society and active in the Canadian Tuberculosis Association and the Laennec Society of Ontario. In addition to his Canadian affiliations, he was a member of many other medical bodies, including the American College of Physicians, the American College of Chest Physicians, American Academy of Allergists, and the American Board of Internal Medicine. He was a member of the Senate of the University of Toronto from 1944, President of the Medical Alumni Association of the University in 1945-1946, and included among his activities those of the Church and philanthropic bodies.

The profession in Canada has suffered a severe loss in his untimely death.

HAROLD I. KINSEY

## BOOKS

JOHN FRANCIS *Bovine Tuberculosis Including a Contrast with Human Tuberculosis* Pp 220 (Foreword by J R M Innes), 1947, Staples Press, Ltd, London, Price, 25s

The program for the eradication of tuberculosis among cattle in the United States was initiated in 1917. The results of this tremendous undertaking in the control of a major infectious disease have been amazingly good, and constitute a notable conquest of an animal disease of great economic and public health importance. However, physicians and others concerned with the epidemiologic aspects of tuberculosis in human beings often lose sight of the fact that in certain other parts of the world tuberculosis of cattle still remains a tremendous economic burden on agriculture and a constant threat to human health.

Francis' book, which is the subject of this brief review, should serve as a reminder that bovine tubercle bacilli are capable of severe and even fatal infections in human beings and that tuberculosis in man cannot be eliminated or even satisfactorily controlled unless the disease in cattle is subjected to measures that will eventually lead to its eradication. Since there has been no recent adequate review of bovine tuberculosis on a world-wide basis, Francis has accomplished an important task in providing a great mass of information pertaining to the disease in its natural and in other susceptible hosts. In addition, the detection and control of the infection in cattle are considered.

The subject matter of the book is divided into six major subdivisions. These include the incidence of tuberculosis of cattle and the economic loss occasioned by the disease, a consideration of the pathogenesis of bovine tuberculosis in the natural host (this is prefaced by a brief discussion of the important differences between the development of tuberculosis in human beings and in different species of animals), tuberculosis of bovine origin in man, detection of tuberculous cattle by tuberculin and by other means, vaccination of cattle with BCG and with the vole bacillus, and lastly, the control of bovine tuberculosis.

A valuable feature of the book is the well-written summary that concludes each subdivision. This idea has been extended to an over-all summary of the entire book, in which the author has succeeded in condensing into four and one-half pages the most important facts which his admirable review has revealed.

Francis concludes that the incidence of tuberculosis among all the cattle of Great Britain is between 17 and 18 per cent. However, he states that the incidence of the disease is higher among dairy cattle, where the average incidence is about 25 per cent. The data indicate that the incidence increases with the extension of age, in infected herds, 40 per cent of the animals five to six years of age may be infected. (By comparison, at present the incidence of tuberculosis in the cattle population of the United States is less than 0.5 per cent.)

As to the occurrence of bovine tubercle bacilli in the milk in Great Britain, Francis states that "about eight per cent of raw churn milk and nearly all of the 3,000 gallon tanks, in which raw milk is frequently brought to our large cities, contain tubercle bacilli." Francis believes that in Great Britain 5 per cent of all human deaths due to tuberculosis are due to infections caused by the bovine type of the tubercle bacillus. Of children less than 5 years of age who die of tuberculosis, the incidence of infection due to bovine tubercle bacilli is considered to be 30 per cent. The extension of pasteurization to include all milk used for human consumption would at least protect human beings from this infection.

Since 1935 the veterinary profession and dairy owners of Britain have made a creditable beginning in establishing "attested" or tuberculosis-free herds. It is estimated that at the present time approximately 10 per cent of the cattle in Great Britain are in herds "attested" as being free of tuberculosis. Perhaps when the true significance of tuberculosis of dairy cattle is fully appreciated by the consumer of milk and dairy products the final conquest of bovine tuberculosis in Great Britain will not be long delayed.

Francis has contributed to the solution of the problem by assembling the facts. What use is made of them will depend on how insistent the British public becomes in demanding the correction of the shocking evils that perpetuate the distribution of misery and death in milk containers.

Francis completes his review by listing 400 selected references from the world's literature. This is followed by a useful and apparently correct and adequate index.

This book is truly an indispensable reference for physicians, public health workers, and veterinarians who are expected to be informed concerning an extremely important disease of cattle which so long as it exists constitutes a menace to human welfare. The book should focus attention on the fact that tuberculosis is a disease of many different species and that a heterologous infection can be as important to the human patient as a homologous one.

W H FELDMAN

ROBERT COOPE *Diseases of the Chest, Second Edition, Pp 541, The Williams & Wilkins Company, Baltimore, 1948, Price, \$7 50*

This book is written for medical students and general practitioners. It presents a well-balanced combination of anatomical, physiological, and pathological considerations with clinical aspects of diseases of the chest. The reader obtains a well-rounded picture of respiratory diseases by equal emphasis of the above stated factors. Considerable attention is paid to the social and economic factors of respiratory diseases. The discussion of the social aspects of tuberculosis, for instance, is well worth being read not only by the general practitioner but also by every worker in this field. The book contains only a small number of radiograms as the author takes the viewpoint that radiology should be taught in hospital practice in relation to patients studied by the student himself. The few chest films included at the end of the book are of good technical quality.

Some therapeutic chapters are not quite up to date. Significant advances, such as the antibiotic treatment and excisional therapy of tuberculosis, are not mentioned. Beryllium poisoning and histoplasmosis, diseases more intensively studied in this country in recent years, should be included in future editions.

The reading of the book is made easy by the vivid and stimulating style of the author. The medical student will find this book the logical continuation of his preclinical training in the anatomy and physiology of the respiratory tract while the general practitioner should welcome the opportunity to refresh his knowledge in this field by the thorough presentation of the various factors involved in each disease.

HANS ABELES

ESTHER LUCILE BROWN *Nursing For The Future. A report prepared for the National Nursing Council. Pp 198, Russell Sage Foundation, New York, N Y, 1948, cloth, \$2 00*

This report is the omega and alpha of an examination of the question of who should organize, administer, and finance professional schools of nursing. The study completes

part of one sector of the program for nationwide action in nursing proposed by the National Nursing Council as an outgrowth of cooperative activity of nursing organizations during World War II. The study was undertaken in the hope that impetus might be provided for redirection of effort.

"The first, and most important, basic decision made during preliminary discussions was to view nursing service and nursing education in terms of what is best for society—not what is best for the profession of nursing as a possibly 'vested interest'."

The director of the study, Dr. Esther Lucile Brown, was released for this important work from her position as Director of the Department of Studies in Professions of Russell Sage Foundation. In 1940 she had written a book, *Nursing as a Profession*, and had also participated in studies to determine how "education for an essential profession can be molded to meet the present needs of society." Dr. Brown's rich background has enhanced the value of her report which is an outstanding contribution to nursing as well as to society. The study was financed in part by a grant from the Carnegie Corporation of New York.

In the first two chapters of the report the author vividly portrays the extension of health services and the implications of these changes for the nursing of the future.

She believes the answer to the problem of obtaining a supply of nursing care that is quantitatively and qualitatively sufficient lies in answers to the questions: What kinds of *nursing functions* need to be performed? Can persons be found and prepared to fulfill these *functions* effectively, whether they be graduate nurses or not?

In discussing the future role of the professional nurse, Doctor Brown recommends that the term professional when applied to nursing education and to nurses be restricted to those schools and those nurses able to meet certain defined standards and that nursing make a matter of first importance the examination of all schools, designating and publishing a list of those which meet standards for accredited professional schools.

The final chapters are devoted to a discussion of education for practical and graduate bedside nurses and resources for the future.

The six national nursing organizations have accepted in principle the recommendations in the report *Nursing for the Future* and are working together to promote study and action by lay and professional groups which will help to solve the problems and provide the kind of nursing we all seem to want.

KATHARINE G. AMBERSON



# THE AMERICAN REVIEW OF TUBERCULOSIS

## ABSTRACTS

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### CLINICAL STUDIES, TUBERCULOSIS

**Bronchi in Primary Childhood Tuberculosis**—Three causes of epituberculosis have been proposed: nontuberculous pneumonia, true tuberculosis, and absorption collapse due to pressure of tuberculous nodes. Thirty children were examined bronchoscopically. These included 18 with active primary tuberculosis associated with sharply outlined radiographic shadows of a lobar or segmental type but without mediastinal or tracheal shift, this is the "classical" picture of epituberculosis. In 10 others, the above findings were noted plus a mediastinal shift, this included 2 cases with obstructive emphysema. In the remaining 2, there was bronchiectasis complicating healed tuberculosis. The right side was involved more often than the left. The various bronchial changes were arranged by groups. In type I (9 cases) there was localized bulging of hyperemic mucous membrane. The process sometimes partially occluded the middle lobe bronchus or a branch of the upper lobe bronchus. Thick mucus could intermittently complete the obstruction. This lesion was caused by external pressure of tuberculous nodes. In type IIa (3 cases), the changes of type I were found and in addition there were yellow, glistening, slightly raised areas under the mucous membrane, representing caseous nodes which were "pointing". In type IIb (2 cases), the bulge was more circumscribed and represented a tuberculoma, biopsy of which showed tuberculous tissue. In type IIIa (7 cases), there was an area of ulceration covered by granulation tissue. It is not certain whether a node had eroded or was still "forming". In type IIIb

(5 cases), the bronchus was filled with friable granulation tissue. In type IV (2 cases), no abnormality was seen. In 15 of the 26 cases with positive findings, the carina was widened. In the 2 cases of healed tuberculosis, the findings were a narrowing of the entrance to the middle lobe bronchus in one case and a distortion of the right lower lobe bronchus in the other. The conclusion is that epituberculosis really is absorption collapse secondary to bronchial compression or erosion by tuberculous nodes.—*Bronchoscopic studies in primary tuberculosis in childhood, J N Hutchison, Quart J Med, January 1949, 18: 21*—(A G Cohen)

**Depression of Tuberculin Sensitivity**—Depression of skin sensitivity to tuberculin has been reported previously in patients critically ill with tuberculosis. This study was carried out, in contrast, on patients critically ill with diseases other than tuberculosis as subsequently shown by autopsy examination at the Kansas City General Hospital. Only white patients were tested. The tuberculin used was PPD-S containing 0.0001 mg in 0.1 cc. Histoplasmin prepared by the Public Health Service was employed. The usual proportion of positive reactions to tuberculin and histoplasmin was determined by examining 4,555 apparently healthy persons of all ages. This expected proportion was then compared statistically with the observed reactions in 25 critically ill patients. Among the men, the observed reaction to tuberculin was 10% as compared with the expected 29% and 29% of 25 healthy men. Among the women, the observed reaction to tuberculin was 31% as compared



the expected, between 60 and 79 years, it was 24 per cent, and it fell to 10 per cent in the group over 80 years. Statistics were similar for the women. The results with the histoplasmin reactions were similar except that even between 20 and 39 years the observed reactions among the ill were only 76 per cent of the expected. Almost one-half of those who were insensitive and later recovered showed positive skin tests when they began to improve. The evidence suggests that the depression is nonspecific with respect to the antigen used and the cause of the illness — *Depression of tuberculin and histoplasmin sensitivity associated with critical illness*, M Furcolow, M Engel, & I Bunnell, *Pub Health Rep*, October 1, 1948, 63 1290 — (S Hadley)

**Tuberculoma of the Lung** — Tuberculoma of the lung is defined as "pseudo-tumoral" pulmonary tuberculosis giving spherical, well-circumscribed densities on roentgenograms, usually the sputum contains no tubercle bacilli. Pathologically these tuberculomas do not represent a real entity. Thus, 3 lung specimens removed by lobectomy or pneumonectomy showed 2 different types of disease. In 2 cases the tuberculoma had formed by the confluence of areas of tuberculous bronchopneumonia and of tubercles which were partly or entirely caseated. These were mixed with dense interstitial fibrosis. The third tuberculoma, a round density in the right lower lobe, consisted anatomically of an entirely caseated mass. The caseous material was arranged in concentric layers, each surrounded by a thin fibrous capsule. The origin probably was a central node which gradually enlarged by progressive eccentric caseation. This is considered the more common pathological substratum of tuberculomas — *Étude anatomique et pathologique de tuberculomes du poumon*, P Galy, M Berard, & J Dumarest, *Rev de la tuberc*, 1948, 12 678 — (V Leites)

**Lung Resection for Tuberculosis** — Recent improvements in technique have rendered the surgical removal of tuberculous lung tissue a

somewhat safer procedure than formerly although complications still occur. Since Friedlander's first successful upper lobe removal in 1935, many thoracic surgeons have attempted resections but it is still very difficult to determine the value of such operations. Undoubtedly the results in some cases have been remarkable, many patients have been promptly restored to health without the long and tedious period of convalescence which was necessary after collapse therapy. From 1935 to 1940, the results were discouraging, the mortality following operation varied from 30 to 60 per cent. Beginning about 1942, the results improved as important changes in operative procedure were made, including separate ligation of the blood vessels of the lung stem, suturing and pleuralization of the bronchus, modern anesthesia, and greater use of bronchoscopy, penicillin, and streptomycin. The author usually has used the lateral position with the affected side down and has employed general anesthesia in a closed circuit. When many firm adhesions were present, he has entered extrapleural areas. Of a total of 12 cases, 2 have died and 6 are well, one for more than four years. He removed the apex of the lung for small residual cavities after thoracoplasty in 4 patients, 2 of whom are alive and working. Other surgeons who have resected lung tissue for tuberculosis report mortalities from 5 to more than 50 per cent. The deaths have been due to spread of the disease in the other lung, to empyema, to miliary tuberculosis, to bronchial fistula, and to meningitis. It seems that the value of removal of tuberculous foci by meticulous operative technique has been established but the serious complications and the effects on pulmonary function must be kept in mind. Indications for pneumonectomy, provided the other lung is free from disease, include stenosis of the main bronchus, dilatation of the smaller bronchi, and persistent cavity. Lobectomies are done for basal cavities, tuberculomas, stenosis of the lobe-bronchus, and cavities of the upper lobe which cannot be eliminated by thoracoplasty. If there is any chance that a thoracoplasty may lead to

healing of the lesion without resection, the latter procedure should be postponed—*Les opérations d'extrême dans le traitement de la tuberculose pulmonaire*, Monod, O, *Le Poumon*, November, 1948, 4 327—(A T Lawd)

**Tuberculous Empyema**—The incidence of tuberculous empyema has been increasing since the introduction of artificial pneumothorax. Tuberculous empyema follows artificial pneumothorax in 3 to 20 per cent of the cases and has a mortality rate of 28 to 60 per cent. Treatment includes (1) aspiration and replacement with air only, (2) aspiration and irrigation, (3) oleothorax, (4) thoracotomy, and (5) thoracoplasty. It seems best to remove the pus and irrigate the cavity with Dakin's solution to avoid fistula formation. Twenty-three cases of tuberculous empyema were thus treated with aspiration and irrigation. The empyema followed artificial pneumothorax in 14 cases, effusion in 8 cases, and tuberculous spontaneous pneumothorax in one case. There were 7 cases of minimal pulmonary tuberculosis, 8 cases of moderately advanced, 5 cases of far advanced disease, and 3 without pulmonary lesions. At the end of treatment, 12 patients had their lungs fully expanded and their cavities obliterated, 2 required thoracoplasty, 6 pneumothorax, and one an oleothorax, 2 cases died during treatment. Nineteen patients were followed one to eight years after treatment, 17 were living and working, one was being treated for a pulmonary lesion, one had died from tuberculosis—*Treatment of tuberculous empyema by aspiration and Dakin's solution irrigation*, B H Y T'ang, *Chinese M J*, April, 1948, 66 205—(L Hyde)

**Chest Wall Tuberculosis**—Cold abscesses or chronic discharging sinuses of the chest wall were found in 8 patients of whom 7 had minimal tuberculous lesions in the lungs. Five had sinuses of the chest wall. The belief that tubercle bacilli are carried to the chest wall via the lymphatics was supported by finding tuberculous lymphadenitis in pathologic sections from 6 patients. The disease

should be suspected in any relatively painless, persistent swelling of the chest wall, even if roentgenograms show no bony changes. The diagnosis is established only by demonstrating tubercle bacilli or by finding typical tubercles in the tissues. Removal of the abscess, sinus, and involved bone or cartilage cured 4 of the 8 patients, improved 2, and failed to help the remaining 2—*Tuberculosis of the chest wall*, C, Huang & M Stone, *Chinese M J*, March, 1948, 66 125—(L Hyde)

**Tuberculous Abscess following Penicillin Injection**—A patient developed a tuberculous abscess at the site of penicillin injections. No other tuberculous foci were demonstrated in the body. The lesion is believed to have been hematogenous in origin, though introduction of infection through the needle is a remote possibility—*Tuberculous abscess at site of penicillin injection*, G B Forbes & F G St C Strange, *Lancet*, March 19, 1949, 1 478—(A G Cohen)

#### CLINICAL STUDIES, NONTUBERCULOUS DISEASES

**Intracellular Bodies in Sarcoidosis**—In 1917, J Schaumann described the occurrence of double-contoured, stratified, and sometimes calcified bodies in practically all of the organs from some patients with sarcoidosis. Most authors have considered these bodies to be the products of degeneration of elastic fibrils impregnated with calcium and iron salts. Metchnikoff reported the production of similar bodies by the inoculation of tubercle bacilli into the Algerian gerbil, an animal resistant to tuberculosis. In view of this observation, Schaumann advanced the opinion that tubercle bacilli can be transformed into these structures. The author considers the stratified bodies in Boeck's sarcoidosis to be partly crystalline, globulin precipitates in the cytoplasm. He denies that they are the products of transformed tubercle bacilli and interprets the morphologic lesions in this disorder as representing a serological, hyaline (paramyloid) precipitation having as its starting point a globulin precipitate (allergic hy-

perglobulnoses) in the reticulo-endothelial system. It is highly probable that these precipitates behave as foreign bodies. The hyperglobulinotic reaction is interpreted as expressing an especially high degree of immunity and thus explains the occurrence of stratified bodies in Metchnikoff's inoculation experiments referred to above.—*The nature of the double-contoured and stratified intracellular bodies in sarcoidosis (Boeck-Schaumann), G Telum, Am J Path, January, 1949, 25 85*—(J S Woolley)

**Serology of Sarcoidosis**—It was found that the serum of patients with sarcoidosis could modify or even neutralize the ability of Old Tuberculin (OT) to evoke a typical skin reaction when 9 parts of serum were added to one part of a 1:1,000 dilution of OT. As controls, sera were used from apparently well individuals who showed either a positive or negative Mantoux reaction. Two tuberculin injections were made on the arm of each subject, one containing serum from a control and the other from a patient with proved sarcoidosis. The sera of the sarcoidosis cases almost always showed tuberculin neutralizing powers, occasionally one did not. On the other hand, only an occasional control showed these properties. Thus, the test is not valid for routine diagnostic purposes. The neutralizing powers were weaker after natural remissions, surgical removal of foci, or roentgen therapy. The test was less effective when used on patients with active tuberculosis. The sera were fractionated and it was found that the neutralizing power is in the gamma globulin. Normal gamma globulin does not possess this power. The factor is destroyed by heating at a temperature of 65°C for one hour. It is not affected by soya bean antitrypsin (cf. fibrinolysin).—*A tuberculin-neutralizing factor in the serum of patients with sarcoidosis, A Q Wells & J A H Wythe, Lancet, March 12, 1949, 1 439*—(A G Cohen)

**Bronchogenic Carcinoma**—Primary bronchogenic carcinoma was proved in 131 cases observed between 1940 and 1946. The inci-

dence of bronchogenic carcinoma is increasing absolutely and relatively. Of the 131 patients, 125 were men, 6 were women. Eighty-two patients (62.5 per cent) were between the ages of 50 and 70. One hundred eleven (84.7 per cent) died within eighteen months after the diagnosis had been made. In 63 patients the carcinoma was found in the right lung, in 68 cases in the left lung. The carcinoma was of the squamous cell variety in 114 cases and of the adenomatous type in 14. The most important symptoms are cough, present in 100 patients (76.3 per cent), thoracic pain, in 82 (62.5 per cent), sputum, dyspnea, hemoptysis, loss of weight, wheezing, pulmonary hemorrhage, paralysis of the vocal cords, dysphagia, convulsions, or paralysis of central origin. The roentgenogram is the most valuable single means of obtaining an early presumptive diagnosis. Bronchoscopy should be performed in all cases of suspected bronchogenic carcinoma. Further means of diagnosis are aspiration biopsy, exploratory thoracotomy, and cytologic study of bronchoscopically removed secretion. The following methods of treatment are used: (1) bronchoscopic removal of tissue with forceps and/or with electrocoagulation, (2) irradiation, (3) surgical removal of the involved lung.—*Primary bronchogenic carcinoma. Correlation of recent literature with one hundred and thirty-one proved cases, J J O'Keefe, Arch Int Med, October, 1948, 82 345*—(G C Leiner)

**Sputum Smears for Carcinoma**—Two hundred cases in which a diagnosis of carcinoma was made on the basis of examination of smears of sputum or bronchial secretions were analyzed. In 190 cases a final diagnosis of primary or metastatic pulmonary carcinoma was made. In 4 cases a carcinoma in the esophagus, larynx, or trachea was demonstrated. In 4 cases the examination was proved to be falsely positive. In the remaining 2 cases the final diagnosis was uncertain. Exfoliated carcinoma cells in sputum or bronchial secretions provided the only preoperative microscopic evidence of cancer in 29 of 74 cases of bronchogenic carcinoma in which surgical

exploration was carried out Sputum and bronchial secretions have proved equally satisfactory in the cytologic diagnosis of cancer of the lung, bronchial secretions have the advantage of better localization of the lesion If no sputum is available or if no bronchial secretions can be aspirated, bronchial washing may be required—*Diagnosis of carcinoma of the lung, the value of cytologic study of sputum and bronchial secretions, L B Woolner & J R McDonald, J A M A, February 19, 1949, 139 497*—(H Abeles)

**Thymoma**—A patient who was suspected of having tuberculosis subsequently developed a right mediastinal opacity and a bloody pleural effusion Autopsy revealed a light yellow tumor in the anterior mediastinum compressing the right bronchus, lung, heart, and larger blood vessels There were no metastases to regional lymph nodes Microscopic examination of the tumor showed it to be mostly necrotic The tumor cells were polymorphic with many large reticulum cells, sometimes arranged in trabeculae resembling deformed Hassall's corpuscles Mitotic figures were rare—*Thymoma. Report of a case, S C Pan, C S Chih, & Y P Chen, Chinese M J, May, 1948, 66 257*—(L Hyde)

**Eosinophilic Granuloma of Rib**—A man aged 46 was found by routine roentgenogram to have a sharply defined area of increased density in the left tenth rib There was no blood eosinophilia Seven years later, there was no change in size or appearance of the lesion In the eighth year, he developed persistent pain in the region of the swelling and one year later it was removed Histological examination showed an eosinophilic granuloma Review of the literature shows reports of 46 previous cases ranging in age from one month to 39 years Most were in children The present patient is the oldest in whom the condition has been reported—*Eosinophilic granuloma of rib, A R Grant, R K House & W B Crandell, New England J Med, April 7, 1949, 240 541*—(A G Cohen)

**Scoliosis and Cardiac Failure**—A 19 year old white girl with scoliosis due to anterior poliomyelitis, first noted at the age of 5, died from cardiorespiratory insufficiency The following explanation is made "Important effects of thoracic deformity are to limit pulmonary ventilation, to impede the pulmonary circulation, and to alter respiratory fluctuations in blood flow Increased ventilatory effort, tachycardia, and right ventricular dilatation and hypertrophy are thereby induced If these responses can be considered compensatory, they are inadequate to permit normal development and activity and they ultimately fail completely Treatment is largely preventive, and begins with prevention or correction of the thoracic deformity itself"—*Scoliosis and cardiac failure, W T Hill, Am Heart J, March, 1949, 37 485*—(G C Leiner)

**Pneumonia in Hemolytic Anemia**—A 20 year old woman died with an acute hemolytic anemia of unknown cause, pneumonia in the right lower lobe, acute nephritis, and thrombophlebitis of the left iliac vein The autopsy examination showed disseminated fibrinoid arteritis, nephritis, and an atypical pneumonia of the right lower lobe The pneumonia was characterized by the presence of a peculiar interstitial infiltrate, consisting of plasma cells, lymphocytes and large mononuclear leukocytes Many of the alveoli contained fibrin Fibrin plugs were seen in the alveolar capillaries and there were intra-alveolar hemorrhages There were numerous megakaryocytes in the alveolar capillaries No microorganisms were found—*Acquired acute hemolytic anemia of unknown cause Report of a case with fibrinoid arteritis, atypical pneumonia and lower nephron nephrosis, L J Rather, Arch Int Med, December, 1948, 82 578*—(C G Leiner)

**Lymphogranuloma Venereum**—An 18 year old Negro complained of malaise, anorexia, cough, precordial pain, loss of weight On physical examination a pericardial friction rub was heard and a single enlarged superclavicular

ular lymph node was found. A chest roentgenogram showed enlargement of the hilar lymph nodes. The Frei test and the complement fixation test for lymphogranuloma venereum were positive. Histologic study of the supraclavicular lymph node showed the characteristics of lymphogranuloma venereum. The specific virus was isolated from this node — *Lymphogranuloma venereum in a patient with mediastinal lymphadenopathy and pericarditis. Isolation of the virus from the supraclavicular lymph node*, W H Sheldon, M J Wall, J DeR Slade, & A Heyman, *Arch Int Med*, October, 1948, 82 410 — (G C Lerner)

**Epidemic Pleurodynia** — Between July and October, 1947, 114 cases of epidemic pleurodynia were observed at the Boston City Hospital. The age of the patients was from 3 to 69 years, 80 per cent being less than 30 years old. There were 77 men and 37 women. The onset of the illness was sudden in most cases with pain as the first symptom. Pain only in the chest occurred in 55 patients, in the chest and in the abdomen in 42, only in the abdomen in 16, only in the lumbosacral region in one. Headache was common, cough, anorexia, diarrhea, and chills also occurred. The patients had fever between 99° and 104°F. Other findings were splinting of the chest, pleural friction rub, tenderness of abdomen or chest, slight to moderate enlargement of one or more groups of lymph nodes, pharyngitis, and tonsillitis. Roentgenographic examinations of the chest revealed no abnormalities. Leukopenia with eosinophilia was observed in some cases. Pericarditis, orchitis, and involvement of the central nervous system appeared as complications. The administrations of penicillin and streptomycin had no effect on the course of the disease. Attempts to isolate the etiologic agent gave no results — *Epidemic pleurodynia. Clinical and etiologic studies based on one hundred and fourteen cases*, J F Finn Jr, Th Weller & H R Morgan, *Arch Int Med*, March, 1949, 83 505 — (G C Lerner)

**Chronic Bronchitis** — Chronic bronchitis is characterized by cough, expectoration, and dyspnea. These symptoms may be constant or intermittent. The author believes that in most cases the condition is really a mild form of asthma. In older people, left ventricular failure must be ruled out. Other conditions from which it must be differentiated are sinusitis, bronchiectasis, cystic disease, abscess, carcinoma, and tuberculosis. Asthma is the essential element in all cases and is often allied with vasomotor rhinitis. There are many children who are prone to bronchitis, this later wears off unless the individual is subject to unusual stresses, such as military service. Generalized emphysema is the end result and is the proof of the previous existence of bronchial spasm. Infection is most often secondary. Therefore, given a patient with so-called chronic bronchitis, the first step is to exclude other diseases. The purulent infection should be considered as secondary and treated with antibiotics. Then the primary condition must be treated with antispasmodics and breathing exercises — *Chronic bronchitis*, W A Lister, *Lancet*, April 30, 1949, 1 719 — (A G Cohen)

**Tropical Eosinophilic Asthma** — Tropical eosinophilic asthma is characterized by chronic bronchitis with nonseasonal nocturnal paroxysmal cough, dyspnea, leukocytosis, and high eosinophilia. The disease may last for many years. The etiology is unknown. Administration of arsenicals causes aggravation of symptoms which is followed by complete recovery. Three cases of tropical eosinophilic asthma have been reported previously. Two new cases are described in this paper and a third case is mentioned in a note. All patients had been in the South Pacific area — *Tropical eosinophilic asthma, report of two cases*, I Fond & P Ravenna, *Arch Int Med*, November, 1948, 82 422 — (G C Lerner)

**Fluids for Bronchial Asthma** — Intravenous use of dextrose is indicated in the severe status asthmaticus patient in whom fluids by mouth

are not well tolerated or in those patients in whom orally administered fluids reflexively produce severer asthma. Contraindications to the use of dextrose are minimized by the use of a 5 per cent solution in distilled water. Not more than 500 cc per hour and 3,000 cc in a twenty-four hour period should be administered—*Intravenous use of fluids in bronchial asthma, J M Sheldon, J A M A, February 19, 1949, 139 506*—(H Abeles)

**Pulmonary Complications of Dysphagia**—Mechanical dysphagia complicated by pulmonary lesions was present in 39 cases from the literature and in 9 from the author's series. This was caused by the aspiration of esophageal contents into the bronchial tree. The mechanism varied with different lesions. Carcinoma of the upper third of the esophagus was very likely to produce dysphagia, especially when there was vocal cord paralysis. Aspiration was less likely with neoplasms of the lower two-thirds. The most frequent lesion complicated by pulmonary changes was achalasia of the cardia, aspiration occurring only during sleep. Pharyngeal diverticulum was also a frequent cause. Aspiration of esophageal contents differs from ordinary aspiration from the upper respiratory tract and mouth in that it occurs in small spills and the aspirated material is less likely to contain organisms. The pulmonary lesions observed were lung abscess in 18 cases, bronchiectasis in 6, fibrosis in 10, lipoid pneumonia in 4, "pneumonitis" in 8, and collapse in 2. There was no hard and fast boundary between these lesions, one type often merged into the other. Tracheobronchitis often preceded the appearance of frank pulmonary lesions. "Pneumonitis" in this article refers to nonspecific inflammation of the lung, it often occurred separately or in association with fibrosis or lung abscess. The aspirations responsible were minimal, sporadic, and of short duration. Pulmonary abscesses were seen most often on the right and in the upper lobes. They were usually the result of a major spill from the esophagus. Prolonged as-

pirations over many years gave rise to fibrosis which often was an end stage of pneumonitis or lung abscess. A typical roentgenographic picture was that of bilateral midzonal fibrosis, more extensive on the right and often sharply demarcated below by the fissures. There was very little disability. Lipoid pneumonia was the result of prolonged aspiration of oily substances such as mineral oil. The picture was similar to that of fibrosis with the additional feature of oily deposits. Collapse was due either to aspiration of a large bolus or to pressure by the enlarged esophagus. Clinically, the cases were arranged in 3 groups: (1) major pulmonary and minor dysphagic symptoms, (2) dysphagia with later development of pulmonary lesions, and (3) a few cases in which the symptoms appeared about simultaneously. There were 18 cases in group one. Cough was the chief symptom. Eight cases of "silent" dysphagia formed an important subgroup in which there was definite obstruction to normal deglutition but no subjective difficulty in swallowing. Group 2 contained 26 cases. In achalasia, the average duration prior to the appearance of pulmonary symptoms was 10 years. The dysphagia usually was minimal or periodic but regurgitation was common. In carcinoma and stricture, symptoms appeared sooner. In younger patients, bronchiectasis was more likely to appear than abscess. Acid-fast bacilli found in the sputum often were nonpathogenic types derived from food. In group 3, consisting of 4 cases, pulmonary and dysphagic symptoms appeared almost simultaneously—*The pulmonary complications of dysphagia, J R Belcher, Thorax, March, 1949, 4 44*—(A G Cohen)

**Lipoid Pneumonia**—The insidious development of pulmonary changes in individuals who take mineral oil for prolonged periods of time has been demonstrated. Faulty deglutition is not essential. A proliferative type of pneumonia develops and sometimes takes on the appearance of a circumscribed tumor. When the tissues are examined, free oil is found in the alveoli. The patients exhibit

remarkably few symptoms. In advanced cases, dyspnea and cough develop and the patients may have recurrent infections. The earliest roentgenographic lesion is a patchy infiltration similar to bronchopneumonia, at other times, the lesion has a hard appearance. Later the infiltrations fuse into a diffuse or circumscribed dense shadow. No hilar adenopathy develops. Early lesions clear up if the laxative habit is abandoned, more extensive lesions persist. The condition must be differentiated from other chronic pulmonary diseases, especially cancer. Besides evaluation of the clinical data, two tests are valuable. The first is the examination of the sputum for oil droplets. A fine paper applied to the surface of a collection of sputum will show grease spots. Sputum examined under the microscope after application of scarlet red will show the characteristic stain of the fat droplets. The other test is aspiration biopsy. Fat droplets can be demonstrated in the washings. The best treatment is prophylaxis. In advanced unilateral involvement, particularly with superimposed infection, surgical extrapation may be considered. The author reports 5 cases seen within a two year period in surveys performed on well adults—*Pulmonary hazard of the ingestion of mineral oil in the apparently healthy adult*, L. Schneider, *New England J. Med.*, February 24, 1949, 240 284—(A. G. Cohen)

**Pneumonitis following Bronchography**—A case is described in which there was no immediate untoward reaction following bronchography. About fourteen days later, however, the patient developed fever and urticaria, roentgenography showed an extensive pneumonitis which had not been present earlier. All the symptoms gradually subsided. In cases of this sort, a history of familial or personal allergy usually is obtainable. Patients about to undergo bronchography should be questioned about previous reactions to iodides and also should have an intracutaneous test with diodrast. Even if these are negative, reactions may occur. If positive, the need for bronchography should be reviewed. The pro-

cedure may be done, nevertheless, but the patient should be encouraged to eliminate the iodized oil as soon as the test is completed and antihistaminic drugs should be given—*Delayed pneumonitis and urticaria following bronchography*, H. E. Bass, *New England J. Med.*, March 31, 1949, 240 505—(A. G. Cohen)

**Idiopathic Pulmonary Fibrosis**—There are numerous causes of pulmonary fibrosis but idiopathic fibrosis is a rare disease, the diagnosis of which requires the close cooperation of roentgenologist, pathologist, and clinician. The roentgenographic appearance is similar to that of fibrosis of various known causes and there is usually considerable emphysema when the condition is well-developed. The examination should include fluoroscopy to detect abnormal movement of the diaphragm, localized areas of emphysema, and paradoxical motion of the mediastinum. The early stages of the disease may not be distinguishable from numerous other processes. Later, there is an increase in the linear shadows, accompanied by a tendency to nodularity and some impairment in motion of the diaphragm. In the far advanced stage there is marked thickening of the strandlike shadows interspersed with areas of emphysema. In most cases the walls of emphysematous blebs are clearly demonstrated and there is definite limitation of motion of the diaphragm, especially on expiration. Paradoxical motion of the mediastinum, heart, and trachea is also generally noted. In one form of idiopathic fibrosis, the emphysema is out of proportion to the fibrosis. Cor pulmonale is often present but the heart shadow may be poorly seen because of the extensive fibrosis—*Idiopathic pulmonary fibrosis. Roentgenologic findings*, L. L. Robbins, *Radiology*, October, 1948, 51 459—(G. F. Mitchell)

**Interstitial Fibrosis of Lungs**—A 33 year old male printer complained of cough, dyspnea, palpitation, and fatigability. A chest roentgenogram showed fine infiltrates in both lower lobes. Dyspnea, cyanosis, and cough

increased and roentgenograms showed extension of the process throughout both lungs. The patient died with the signs of pulmonary insufficiency. Histologic examination of the lungs revealed thickening of the alveolar septums due to connective tissue proliferation and proliferation of the alveolar epithelial cells. This is a case of acute diffuse interstitial fibrosis of the lungs, which was first described by Hamman and Rich. The etiology of the disease is not known—*Acute diffuse interstitial fibrosis of the lungs*, B. P. Potter & I. E. Gerber, *Arch Int Med*, August, 1948, 82: 113—(G. C. Leiner).

**Granulomatous Nocardiosis**—A new granulomatous disease entity caused by an unusual acid-fast organism is described. The patient was a white child, 34 months old, whose illness began with anorexia, nausea, vomiting, and progressive weight loss about four and one-half months before her death. Her course was afebrile. Shortly after the onset of her illness a mass was noted in the abdomen. An enlarged inguinal node was removed and showed complete alteration of its architecture with proliferation of the macrophages, the cytoplasm of which appeared foamy and granular. These cells contained massive numbers of acid-fast, bacilliform organisms resembling tubercle bacilli. The morphologic, cultural, and biochemical characteristics of this organism were those of a fungus but differed significantly from those of similar fungi. It was considered a new species of the family *Actinomycetaceae*, to which the name *Nocardia intracellularis* was given. In the child this organism produced a pure form of granulomatous inflammation characterized by phagocytosis of the pathogen by reticulo-endothelial cells with proliferation of these cells. In the spleen and lymph nodes the proliferation of macrophages displaced completely the normal structure. There was equilibrium between the organism and its host cell to the extent that massive intracellular parasitism constituted the most distinctive feature of the disease. Comparatively little necrosis occurred, and there was no response on the part

of polymorphonuclear leukocytes or other inflammatory elements customarily found in the common infectious granulomas. *N. intracellularis* produces a nonlethal disease in guinea pigs, rats, and mice. It produces no lesions in chickens, rabbits, frogs, and goldfish. In the experimental animal, *N. intracellularis* provokes a response which differs sharply from the reaction in man. This difference is to be found in the comparatively extensive necrosis and relative paucity of intracellular organisms. The lesions heal rapidly in the experimental animal and are accompanied by the production of sensitivity of the tuberculin type—*Pure granulomatous nocardiosis. A new fungus disease in man due to a hitherto undescribed organism, Nocardia intracellularis, n. sp., including a study of the biologic and pathogenic properties of this species*, J. T. Cuttino & A. M. McCable, *Am J Path*, January, 1949, 25: 1—(J. S. Woolley).

**Pulmonary Actinomycosis**—Actinomycosis is a rare disease, being most frequent among farm workers but occurring in both rural and urban communities. The commonest site of disease is the alimentary tract, especially in the ileocecal region, suggesting the oral route of infection, but the thorax is the primary site in one of 7 cases. The infecting organism in thoracic actinomycosis is usually anaerobic although the aerobic form is responsible for some cases. The thorax may be involved primarily, either by the inhalation of infected material or by penetration through the wall of the esophagus to the posterior mediastinum with spread to the lungs. It may be involved secondarily as a result of spread from cervical actinomycosis, retroperitoneal or hepatic infection, or by hematogenesis dissemination. When the lung is primarily involved, consolidation occurs usually in one of the lower lobes. If the visceral pleura is reached, pleural effusion is produced. The infection may then involve the thoracic wall with an empyema necessitatis. If the posterior mediastinum is infected, the thoracic vertebrae and adjacent ribs may be attacked. Cerebral abscesses



occur frequently as a complication of pulmonary actinomycosis following hematogenous dissemination. Early thoracic actinomycosis causes very slight symptoms such as cough or vague chest pain. Physical examination of the lungs may reveal signs of consolidation or of fluid. Later an abscess of the chest wall may develop. With long-standing infection, the symptoms are those of chronic supuration with fever, anemia, cachexia, and finally amyloidosis. The diagnosis of actinomycosis is certain only when the characteristic sulfur granules have been seen or when the organism itself has been cultivated; secondary infection often makes the laboratory diagnosis difficult. The radiographic findings are varied, depending on the structures of the chest involved, and no characteristic changes may be expected. Three cases of pulmonary actinomycosis are presented. The first had a lung abscess of peculiar type which first suggested the diagnosis. The second case was characterized by multiple abscesses, prominent vascular markings, and dilated bronchi with abundant sputum. The third case had a mediastinal effusion. Aspirated fluid revealed the organism in the third case. All 3 cases responded favorably to penicillin — *Pulmonary actinomycosis*, S F Oosthuizen & N H Fainsinger, *Brit J Radiol*, March, 1949, 22 152 — (B Hyde)

**Coccidioidomycosis** — A two- to five-year follow-up study of 20 veterans of World War II with various residual pulmonary lesions of coccidioidomycosis is presented with the case histories of 13 patients. All patients had lived for some time in the endemic area. The residual lesions were nodular densities, cavities, mottled infiltrations, fibrosis, pleural effusion, and calcifications. There was little or no change in the findings over the period of two to five years. The skin sensitivity to coccidioidin diminished slowly. In one case with disseminated lesions, the coccidioidin skin test was negative. Almost all patients were asymptomatic — *Coccidioidomycosis: Persistence of residual pulmonary lesions*, H

E Bass, A Schoner & R Berke, *Arch Int Med*, December, 1948, 82 519 — (G C Leiner)

**Coccidioidomycosis of Cattle** — Coccidioidomycosis was commonly found affecting the bronchial and mediastinal lymph nodes of cattle slaughtered under Federal inspection in Phoenix, Arizona. No lesions were found outside of the thoracic cavity and none were of sufficient extent to warrant condemnation of the carcass. The disease was present in 13 per cent of the slaughtered cattle. It is impossible to detect coccidioidomycosis in cattle on ante-mortem inspection and it is debatable whether the fungus gains entrance by inhalation or via the digestive tract. *Coccidioides immitis* is prevalent in Arizona where it is dry and dusty. Pathologically the affected lymph node has a bulbous appearance. Cross-section reveals few or numerous circular areas of pathologic tissue, each with a purulent center which may be white to light cream in color. Little or no change is noted in the surrounding lymphoid tissue — *Coccidioidomycosis of cattle in Arizona*, C J Prehal, *J Am Vet M A*, June, 1948, 112 461 — (L Hyde)

**Interstitial Pneumonia in Dogs** — Two canine cases of interstitial pneumonia with giant cells and inclusions are reported. The presence of both cytoplasmic and nuclear inclusions indicates the presence of distemper virus. This pneumonia is different from the typical exudative bronchopneumonia seen in 3 field cases of distemper. The interstitial pneumonia probably is a primary virus lesion while the exudative bronchopneumonia is due to secondary bacterial infection — *Interstitial pneumonia with giant cells and inclusions*, D R Cordy, *J Am Vet M A*, January, 1949, 114 21 — (L Hyde)

#### ANTIMICROBIAL THERAPY

**Streptomycin and Streptokinase for Tuberculous Meningitis** — Necropsy of patients dying of tuberculous meningitis reveals a fibrinous exudate containing tubercle bacilli which streptomycin apparently does not

penetrate It was decided to try streptokinase which is obtained from cultures of hemolytic streptococci When injected alone intrathecally, this substance gave a pleiocytosis comparable to that produced by streptomycin There were no untoward clinical effects It was then given simultaneously with streptomycin sulphate in clinical cases of tuberculous meningitis When streptomycin alone was used, there were 3 recoveries (21 per cent) in 14 cases When the two were combined, there were 11 recoveries (53 per cent) in 19 cases —*Streptomycin-streptokinase treatment of tuberculous meningitis, I A B Calne, Lancet, March 12, 1949, 1 441* —(A G Cohen)

**Streptomycin for Extrapulmonary Tuberculosis**—Streptomycin was used in the treatment of extrapulmonary tuberculous lesions in 92 cases There was significant pulmonary activity in only 2 cases, most of the others had healed residua Many patients had multiple lesions making a total of 157 The earlier doses of streptomycin were as high as 30 Gm a day More recently, the dosage has been 10 Gm daily for 42 days The results of treatment were graded as excellent in 50, good in 36, and failure in 14 per cent There were known recurrences in 8 per cent of the cured group The results were best in cases with sinuses, closure occurred in 67 per cent in an average of 62 days, the other 33 per cent were improved In bone and joint disease, the results were excellent in 35, good in 47 and failure in 18 per cent In genito-urinary disease they were excellent in 52, good in 13 and failure in 15 per cent In 74 per cent of postnephrectomy cases urine cultures were positive initially and turned negative Poor renal function is not a contraindication if the drug is given in small doses There was prompt arrest in 2 cases of lupus vulgaris In 5 cases of adenitis the results were excellent in 2 and good in 3 In 3 cases of peritonitis the results were excellent in one and improved in 2 In 4 cases of mastoiditis the results were excellent in 2 and good in 2 In

4 cases of paraplegia secondary to spinal disease, there was complete cure in 2 and great improvement in one—*Streptomycin in the treatment of extrapulmonary tuberculosis, K Jellinek, New England J Med, April 28, 1949, 240 681* —(A G Cohen)

**Streptomycin for Tuberculous Endometritis**—A woman aged 26 was found to have a positive endometrial biopsy for tuberculosis There was no evidence of tuberculosis elsewhere in the body She received 0.5 Gm of streptomycin twice daily for 129 days and was kept on bed rest Following treatment, curettage showed no evidence of tuberculosis histologically or by culture—*Streptomycin in the therapy of tuberculosis of the endometrium, A Aronson & R W Dught, New England J Med, February 24, 1949, 240 294* —(A G Cohen)

**Streptomycin for Tuberculous Enteritis**—In Veterans Administration hospitals 33 men have been treated with streptomycin for tuberculous enteritis There were 29 white patients, 3 Negroes, and one Mexican The average duration of their tuberculosis was nineteen months and all had far advanced pulmonary tuberculosis Intestinal symptoms had been present four to six months prior to treatment Intramuscular injections of 10 to 20 Gm of streptomycin were given daily, at present 10 Gm in 2 doses is recommended Oral treatment was employed in 2 cases but four to six weeks elapsed before complete relief was obtained compared to one week when intramuscular treatment was used Treatment usually was given for 60 to 120 days, 6 patients were treated only fourteen days The drug uniformly relieved symptoms almost immediately Increased appetite was noted first In a few days there was loss of abdominal tenderness, rigidity, and distention The temperature dropped to normal and there was a weight gain proportional to the previous weight loss Tubercle bacilli disappeared from the sputum in only 8 cases The pulmonary disease was not greatly improved in the

majority, although 3 patients received thoraeoplasty after recovering from their intestinal disease. A fourteen day course of treatment was employed in 6 cases for the relief of symptoms only, the symptoms recurred in 2 cases. Of those receiving a longer course, 25 patients have been followed for an average of six and one-half months. One patient had 3 recurrences but for seven and one-half months has been symptom-free. His pulmonary disease also appears inactive. Two patients were operated on for acute appendicitis without developing a fecal fistula. One patient with tuberculous enteritis and epididymitis had had a resection of the ileum with a colostomy, he experienced marked relief. Roentgenograms and fluoroscopic reports of 17 patients showed abnormalities before treatment. The appearance returned to normal in 6 patients, 8 showed improvement with some residual deformity. Two patients showed marked residual deformity, one developed signs of a small bowel obstruction and one showed no roentgenographic change in spite of clinical improvement. From the radiological standpoint it was impossible to determine the ideal length of treatment. However, normal roentgenograms can be expected eventually if the abnormalities are primarily those of local irritation. Where ulceration has been deeper, more widespread, and of longer duration, there may be further distortion due to scar contraction. —*Streptomycin in the treatment of tuberculous enteritis. A report of thirty-three cases*, E E Mason, W W Krudelbaugh, W H Crouch, & M Ward, *Am J M Sc*, January, 1949, 217-28 —(G F Mitchell)

**Tuberculosis with Addison's Disease** — A 22 year old woman with tuberculous cavitation received pneumothorax and pneumonolysis despite which bilateral spread occurred. She had increasingly severe nausea, vomiting, and abdominal pain so that she became unable to retain even liquids. There was a rapid loss of 37 pounds. No tuberculosis of the gastrointestinal, urinary, and pelvic organs could be demonstrated and a diagnosis of Addison's disease was made. Treatment with adrenal cortex and streptomycin was followed by

marked improvement within a week. The pneumothorax was maintained. The cavity closed and tubercle bacilli disappeared from the sputum. The Addison's disease may have been brought under control by the streptomycin. —*Active pulmonary tuberculosis together with Addison's disease*, M C Cheney, *J A M A*, April 16, 1949, 139-1077 —(E A Rouff)

**Streptomycin-enhanced M Tuberculosis** — Streptomycin greatly enhanced the growth of one strain of *Mycobacterium tuberculosis*. The organism was obtained from a 33 year old patient on the ninety-sixth day of treatment for advanced pulmonary tuberculosis which had been spreading constantly despite therapy. The organism grew very poorly and slowly in the control tube without streptomycin but luxuriantly in tubes of either Dubos-Davis or Lowenstein-Jensen medium containing 10  $\gamma$  to 1,000  $\gamma$  of streptomycin per cc. Growth at 1,000 was less striking but much greater than the control. This observation was duplicated in 5 of 7 trials. Another sputum sample was obtained four months later. The bacilli from this specimen would not grow in a medium without streptomycin but showed good growth on slants containing 1, 10, or 100  $\gamma$  of streptomycin per cc. —*Enhancement of growth of a strain of M tuberculosis (var hominis) by streptomycin*, G Spendlove, M Cummings, W Fackler, & M Michael, *Pub Health Rep*, September 3, 1948, 63-1177 —(S Hadley)

**Streptomycin-resistant Tubercle Bacilli** — A large proportion of tuberculous mice, treated with amounts of streptomycin which permitted a relatively long survival time, yielded streptomycin-resistant tubercle bacilli. The more streptomycin administered the longer the survival time and also the greater the incidence of streptomycin-resistant strains of tubercle bacilli. —*Occurrence of streptomycin-resistant tubercle bacilli in mice treated with streptomycin*, G P Youmans, E H Williston, & R R Osborne, *Proc Soc Exper Biol & Med*, January, 1949, 70-56 —(F B Seibert)

**Neomycin**—Because of the disadvantages of streptomycin, a search has been continued among the Streptomycetes for a compound which would be effective against the streptomycin-resistant bacteria, especially *M tuberculosis*. Neomycin seems to be such an agent. It is a basic compound, most active in alkaline solution. It is soluble in water, insoluble in organic solvents, and is thermostable. It is active against numerous gram-positive and gram-negative bacteria, especially *Mycobacterium*, but not against fungi. It displays similar activity against streptomycin-sensitive and streptomycin-resistant bacteria and considerable activity against *M tuberculosis*. It has little or no acute toxicity to animals.—*Neomycin, a new antibiotic active against streptomycin-resistant bacteria, including tuberculosis organisms*, S A Waksman & H A Lechevalier, *Science*, March 25, 1949, 109: 305—(E A Rouff)

**Lupulon**—Lupulon, a fat-soluble antituberculous agent derived from hops, was effective *in vitro* in a dilution of 1:40,000. When given orally or intramuscularly it was active against experimental mouse infections of *M tuberculosis*. Treatment with lupulon effected a reduction of approximately 4 to 1 in the numbers of acid-fast organisms in the lesions of animals infected with the H37Rv strain over those not treated. The LD<sub>50</sub> on a single intramuscular injection was 600 mg per Kg in mice, on a single oral administration it was 1,500 mg per Kg.—*Antituberculous activity and toxicity of lupulon for the mouse*, Yin-Ch'ang Chin, H A Anderson, G Alderton, & J C Lewis, *Proc Soc Exper Biol & Med*, January, 1949, 70: 158—(F B Seibert)

**Salicylate = PAS Antagonism**—The bacteriostatic effect of para-aminosalicylic acid (PAS) was antagonized by high concentrations of salicylic acid. This effect of the salicylate was highly specific and not shared by related compounds. In one experiment it was shown that one mole of PAS was antagonized by 4 to 12 moles of sodium salicylate. One mole of para-aminobenzoic acid also abolished the effect of 4 moles of PAS.

Pantothenic acid did not inhibit the tuberculostatic effect of salicylate.—*Antagonism between effects of p-aminosalicylic acid and salicylic acid on growth of M tuberculosis*, G Iránovics, *Proc Soc Exper Biol & Med*, March, 1949, 70: 462—(F B Seibert)

#### LABORATORY STUDIES

**Specific Serum Agglutination of Erythrocytes**—Red blood corpuscles can adsorb various substances and thereby can be rendered specifically agglutinable by an antibody directed against the substance adsorbed. The authors observed that the sera of tuberculous experimental animals and of tuberculous patients can agglutinate erythrocytes previously treated with aqueous extracts of tubercle bacilli or with products from their culture filtrate. Washed, packed sheep red cells were suspended in an excess of an isotonic, neutral, dialyzed solution of a crude polysaccharide fraction of tubercle bacilli. This was prepared by extracting the bacilli with aqueous dibasic phosphate solution after exhaustive extraction with 88 per cent phenol solution. When incubated with this extract, the red cells adsorbed the polysaccharide material. The red cells then were washed with isotonic saline solution and resuspended in 0.5 per cent concentration in saline for use as "sensitized cells" in the hemagglutination test. The serum to be tested was first heated to inactivate complement and then treated with approximately one-fifth of its volume of washed, packed, unsensitized sheep cells. This treatment was repeated in order to remove any nonspecific antibodies which might agglutinate unsensitized cells. The hemagglutination test was performed by adding to dilutions (1:8 to 1:1,024) of the treated serum an equal volume of the 0.5 per cent suspension of sensitized red cells. Appropriate controls were included in each test. The sera of rabbits injected with BCG showed varying potencies when tested. All showed some agglutination in a dilution of 1:80 and several agglutinated at 1:1,280. The sera of patients with active pulmonary tuberculosis gave agglutination in dilutions of 1:8 to 1:32. One patient with milary tuber-

culosis had a titer of 1 256 None of the sera from nontuberculous individuals, including Wassermann-positive specimens, gave titers higher than 1 4 One sample of deglycerinated OT was found capable of sensitizing the sheep erythrocytes, showing that at least one substance responsible for sensitization is heat-stable and is present in the filtrate of cultures of mammalian tubercle bacilli Experiments in which the carbohydrate and the protein fractions of bacillary extracts and culture filtrates were used to inhibit the specific hemagglutination demonstrated that the material responsible for the hemagglutination resides in the polysaccharide fraction, very small amounts of this fraction could be detected by this technique Extracts of virulent and avirulent bacilli were equally effective in sensitizing the red cells The antibody responsible for this hemagglutination test circulates in the blood of immunized animals and of human beings with active tuberculosis The test exhibits a high degree of specificity and, in particular, does not give rise to any cross-reaction with Wassermann-positive sera as sometimes occurs in the case of the complement fixation reactions in tuberculosis The specific hemagglutination reaction can be inhibited by adding the soluble reactive antigen to the serum before introducing the sensitized red cells into the system Under these circumstances the soluble antigen, if present in sufficient amount, combines with its corresponding antibody and prevents it from agglutinating the sensitized erythrocytes This inhibition test, when utilized together with the agglutination test proper, permits the quantitative detection of very small amounts of the sensitizing antigen It will be interesting to test whether this technique permits the detection of specific antigen circulating *in vivo*—*Specific serum agglutination of erythrocytes sensitized with extracts of tubercle bacilli*, G Middlebrook & R J Dubos, *J Exper Med*, November 1, 1948, 88 521 —(J S Woolley)

**Nucleoproteins of Avian Tubercle Bacilli** — Crude nucleoprotein was best extracted from ether-washed, dry tubercle bacilli of the avian

strain by grinding them for 30 minutes with glass powder and borate buffer at pH 8.3 and then shaking them in the cold with this buffer for two days The extracts, after centrifuging, were dialyzed against water Glycogen was removed by sedimentation at 31,000 g and then the supernatant was again dialyzed and dried in a vacuum from the frozen state It was further found that a nucleoprotein fraction flocculated around pH 4.0 but failed to precipitate in half-saturated ammonium sulfate at pH 6.3 It contained mostly desoxy-pentose nucleic acid Attempts to isolate the nucleic acid from the nucleoprotein by means of proteolytic enzymes, disintegration by prolonged dialysis against molar sodium chloride, or precipitation with lanthanum nitrate were not successful Cleavage with saturated sodium chloride was partially effective but it was more successful with sodium desoxycholate Further purification was made by means of electrophoresis through which a nucleic acid fraction of 6.6 mg was obtained This fraction contained 12.9 per cent nitrogen and 7.6 per cent phosphorus—*On the nucleoproteins of avian tubercle bacilli*, E Chargaff & H F Sadel, *J Biol Chem*, January, 1949, 177 417 —(F B Seibert)

**Nucleic Acid of Avian Tubercle Bacilli** — Desoxypentose nucleic acids derived from avian tubercle bacilli and from yeast were found to contain the purines, adenine and guanine, and the pyrimidines, cytosine and thymine No 5-methyl-cytosine could be detected in the nucleic acid of the tubercle bacilli The sugar components of both nucleic acids, released by the hydrolysis of the enzymatically produced nucleosides, were found to be identical with the desoxypentose of thymus nucleic acid, *i.e.*, 2-desoxyribose The pentose nucleic acid of the tubercle bacillus was shown to contain ribose—*Microbial nucleic acids The desoxypentose nucleic acids of avian tubercle bacilli and yeast*, E Vischer, S Zamenhof, & E Chargaff, *J Biol Chem*, January, 1949, 177 429 —(F B Seibert)

**Test for Histoplasmosis**—A complement fixation test has been studied previously in the guinea pig and in test 500 human sera. The technique was essentially that of the Kolmer test. Of 9 proved cases of histoplasmosis 67 per cent had positive complement fixation reactions and 22 per cent showed doubtful reactions. Among 13 cases in whom the skin test for histoplasmosis had changed from negative to positive during a period of observation, 15 per cent of the complement fixation tests were positive and 77 per cent were negative. In a group of 36 persons who had untreated pulmonary lesions with a positive histoplasmin skin test and a negative tuberculin, 17 per cent were positive, 11 per cent were doubtful, and 72 per cent were negative. A control group of 212 persons showed no positive reactions, 54 per cent doubtful reactions, and 94.6 per cent negative reactions. It is too early to draw definite conclusions but the test may prove to be useful in the study of histoplasmosis infections.—*A Complement Fixation test for histoplasmosis*. II. *Preliminary results with human sera*, M. L. Fircroft, J. L. Burnell, & D. I. Tenenbergh, *Pub. Health Rep.*, February 6, 1948, 63: 165—(S. Hadley)

**Pulmonary Anoxemia**—Studies of respiratory and circulatory functions were made in 18 patients with different degrees of pulmonary fibrosis and emphysema. Alveolar carbon dioxide tension was increased, alveolar oxygen tension was decreased. Due to unequal ventilation, the composition of the alveolar air is not uniform in the emphysematous lung. The ventilation rate was slightly increased, which may be due to cardiac decompensation or to the asphyctic stimulus. The total pulmonary capacity was slightly decreased. The average tidal air, the vital capacity, and the complementary air were less than normal, but the reserve air was about normal. The residual air and functional residual air were increased. The basal metabolic rate was increased in some cases. The oxygen capacity of the blood was increased in most cases. There was a coarse correlation between the degree of anoxia and

the response of the bone marrow. The hemoglobin content per 100 cc. of red cells was lower than in normal subjects at sea level or at high altitude. Although the oxygen content of the arterial blood was slightly increased, oxygen saturation and pressure were below normal. The alkaline reserve was normal in whole blood, increased in plasma. The total carbon dioxide content and pressure of the arterial blood was increased, the pH was decreased. The difference between alveolar and arterial oxygen pressures was considerably increased but the difference between the carbon dioxide pressures was only slightly increased. Oxygen breathing caused a decrease in the ventilation and in the blood oxygen capacity, an increase in the difference between alveolar and arterial oxygen, a rise in the arterial carbon dioxide pressure, a decrease of the arterial pH, and a diminished heart rate. Breathing of carbon dioxide caused a smaller increase in the ventilation than in normal persons. An elevated venous pressure was found only when cardiac insufficiency was present. Lifer and decholin circulation times were increased in most cases. The blood volume usually was increased due chiefly to an increase in the erythrocytes. The cardiac output was diminished in cases with cardiac insufficiency.—*Respiration and circulation in pulmonary anoxemia*, A. C. Taquini, J. C. Fasco'o, J. R. E. Suarez & H. Chiodi, *Arch. Int. Med.*, December, 1948, 82: 554—(G. C. Leiner)

#### PUBLIC HEALTH AND EPIDEMIOLOGY

**Tuberculin Reactions in the Aged**—Tuberculosis tests were performed in 1947 on 257 unselected boarders at a Parisian home for the aged. Only 17 persons (6.6 per cent) had a negative reaction to a Mantoux test, using a 1:100 dilution of tuberculin, only 14 persons had a doubtful reaction. In the age group of 60 to 69 years, 4 per cent gave a negative reaction, in the group 70 to 79 years, 7 per cent, and in the group 80 to 102 years, 6.9 per cent had a negative reaction. This raises a question as to "anergy" due to old age.—*Les réactions tuberculiques cutanées dans un hospice*

*parisien de vieillards, Ch Coury & P Marland, Rev de la tuberc, 1948, 12 391 —(V Leites)*

#### Chest Roentgenograms in Tuberculosis —

The clinical significance of minor pulmonary infiltrates cannot be determined with accuracy from the chest roentgenogram and each case must be considered individually. The early diagnosis of tuberculosis depends upon the recognition and evaluation of nodular infiltrates usually located at the apex of the lung anterior to the plane of the first rib and slightly above it. The majority of these infiltrates heal, but small caseous areas unpredictably may produce fresh lesions by bronchiolar emboli. A single negative bacteriologic examination does not mean that dangerous numbers of bacilli will not be excreted later and frequent chest roentgenograms are probably the most reliable method for following minimal infiltrates. Tuberculosis undoubtedly spreads from apical foci with greater frequency in Negro than in white patients, but chest roentgenograms should be repeated every three months in any patient with a minimal infiltrate. Apical lesions in older males must be observed carefully since it is now apparent that these lesions may progress in individuals whose resistance is affected by metabolic, degenerative, and other changes accompanying advancing age. Annual

roentgenograms of the chest should be a minimum recommendation for these patients. To feel falsely secure about any pulmonary infiltrate is dangerous to the patient and may expose others to months of contagion — *The role of the chest roentgenogram in the evaluation of pulmonary tuberculosis, H M Payne, J Nat M A, September, 1948, 40 210 — (L Hyde)*

#### Lung Cancer in Chromate Workers —

Workers in the chromate industry have been studied because of the high incidence of lung and respiratory tract carcinoma that has been noted among them. The group studied included 1,445 employees. The mean duration of exposure to chromates was 14.5 years. Of all the deaths in these men, 21.8 per cent were due to cancer of the respiratory system, this is 16 times the expected rate of 1.3 per cent. In 5 or 6 of the plants studied, the rates in the group over 50 years of age ranged from 20 to 70 times that for a comparable industrial group. One plant which handled only bichromate and chromic acid had no deaths due to carcinoma of the respiratory tract. This suggests that the monochromates may be the compounds responsible — *Cancer of the respiratory system in the U S chromate-producing industry, W Machele & G Gregorius, Pub Health Rep, August 27, 1948, 63 1114 — (S Hadley)*

# THE COST OF RESEARCH ON TUBERCULOSIS IN THE UNITED STATES

Analysis of Allocations in 1947-1948

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## INTRODUCTION

Within the last ten years important scientific discoveries have led to greatly increased appropriations for research in the United States. Investigations in physico-chemical, medical, and other fields were stimulated and intensified by World War II. Establishment of a National Science Foundation, under the auspices of the Federal Government, has been much discussed in recent years and, in 1947, the President's Scientific Research Board made a survey of research under way at that time, its cost, and the future needs for a well coordinated program of scientific research in the United States.

According to Mr. John R. Steelman, Chairman of the President's Scientific Research Board,

As a Nation, we should spend each year no less than one per cent of our national income for research and development in the physical and biological sciences, including medicine. Our present national research and development budget amounts to about one-half of one per cent (1). The Nation as a whole invests only around \$110 million annually for scientific research and development in medical and allied fields, as contrasted with more than 10 times that amount spent for all other forms of scientific inquiry (2).

Mr. Steelman points out further that

The challenge of our times is to advance as rapidly as possible the understanding of diseases that still resist the skills of science, to find new and better ways of dealing with diseases for which some therapies are known, and to put this new knowledge effectively to work (2).

Singularly, this statement represents the philosophy of the Committee on Medical Research of the National Tuberculosis Association in the establishment of a medical research program in the fall of 1920. In his presidential address at the annual meeting of the Association in 1921, Dr. Gerald B. Webb reiterated the principles set down by the Committee when he stated that

We must frankly state our knowledge of the disease, and also the extent of our ignorance regarding tuberculosis, so that we can more wisely guide the efforts made in prevention and cure, and direct research to bring further enlightenment (3).

Stimulated by the findings of the President's Scientific Research Board and by a desire for a more detailed analysis of the cost of investigation in its own field, the Division of Research of the National Tuberculosis Association col-

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lected information on the amount spent for tuberculosis research in the United States. Data were compiled with the assistance of official and voluntary agencies, universities, foundations, pharmaceutical houses, and firms manufacturing X-ray equipment. Although the fiscal year varies with different organizations, the figures used represent funds reported for a twelve-months' period during 1947-1948.

The survey is not exhaustive, but it is hoped it will present sufficient information to be of some value in future planning. There are many intangibles, the cost of which cannot be accurately reckoned, and the greatest of these is personnel. Services within all of the groups mentioned above as well as the cost of buildings and their maintenance, which may indirectly increase the cost of tuberculosis research, represent a sum impossible of calculation. Undoubtedly it is of large size.

#### TYPES OF RESEARCH

Research, according to Mr. Steelman (2), may be categorized as follows: (a) basic, or fundamental research, *i.e.* theoretical analysis, exploration or experimentation, (b) background research, *i.e.*, systematic observation, collection, organization, and presentation of facts, (c) applied research *i.e.*, extension of basic research to the determination of the combined effects of physical laws or generally accepted principles with a view to specific application, and (d) development, *i.e.*, adaptation of research findings to experimental, demonstration, or clinical purposes. This is not a new concept but one which may well bear repeating here.

While "research" in general terms often is assumed to represent investigations of a purely scientific nature, epidemiological, statistical, social and historical research are of considerable importance in the solution of problems for the control of tuberculosis. The principles set down above can, in most instances, be adapted to apply to these fields.

#### PRESENT RESEARCH PROGRAM

##### *Official Agencies*

##### *Public Health Service*

Within the last few years, by far the most extensive program for research in tuberculosis has been that of the Federal Government. Since the establishment of the Tuberculosis Control Division in the United States Public Health Service in 1944, an increasing appropriation of funds for tuberculosis control has been made. It was reported that in the last fiscal year (1947-1948) a sum of \$300,000 was allocated to the Field Studies Section of the Division for statistical and epidemiological research, and \$43,529 appropriated for the Tuberculosis Evaluation Laboratory, set up within the last few years in Atlanta, Georgia, the primary purpose of which is to standardize laboratory procedures for the detection of tuberculosis.

In the National Institutes of Health late in 1946, an enlarged program of in-

vestigations was set up, stimulated by early studies of a group of investigators in the American Trudeau Society, Medical Section of the National Tuberculosis Association (4, 5) A Tuberculosis Study Section, composed of specialists in the field, was organized primarily for the purpose of evaluating the effectiveness of streptomycin in the treatment of tuberculosis through establishment of research grants to qualified investigators (6) During the fiscal year 1947-1948, reports show that 31 grants for laboratory and clinical studies were approved, amounting to \$589,700 In addition, \$250,000 was set aside for the estimated cost of the streptomycin, and \$80,000 for fellowships A Central Coordination and Analysis Office was established to correlate and analyze the findings of the various clinical investigations for an evaluation of the therapeutic value of streptomycin in tuberculosis In addition to these studies, the Division of Infectious Diseases of the National Institutes of Health continued its investigations of various chemotherapeutic agents and the relation of histoplasmosis to pulmonary calcification, synthesis and testing of commercial compounds and antibiotics, and the synthesis of new drugs and their synergistic action with antibiotics such as streptomycin For this research approximately \$94,800 was budgeted in the above period, according to data received

The total expenditure reported for the tuberculosis research program of the Public Health Service for the fiscal year 1947-1948 amounted to approximately \$1,358,029, with \$934,500 devoted to investigations with chemotherapeutic agents

#### *Department of Agriculture*

The Bureau of Animal Industry, United States Department of Agriculture, carried out studies of the tubercle bacillus and other acid-fast organisms affecting bovine and avian species at a reported cost of \$26,300 for the 1947-1948 fiscal year

#### *Department of the Interior*

In the United States Department of the Interior, the Office of Indian Affairs stated that \$50,795 was allocated in the same period for experimental investigations with BCG in certain segments of the Indian population

#### *Department of the Army*

The Army tuberculosis research program included a study of minimal tuberculosis in a group of 1,100 cases at Fitzsimons General Hospital, with an annual budget of \$28,552, exclusive of the cost for military personnel In addition, the cost of streptomycin for experimental investigations was \$160,200 Studies of the relation of nutrition to tuberculosis in the Medical Nutrition Laboratory at Chicago were made at a cost of \$9,000 Administrative expense in the central office for personnel engaged full time in tuberculosis research, as well as advisory service procured from the National Research Council, amounted to \$30,000

In accordance with the foregoing figures, the total reported cost of the Army program for tuberculosis research in the 1947-1948 period was \$227,752.

*Navy Department*

The United States Navy, through its Office of Naval Research, awarded several grants for tuberculosis research during the 1947-1948 fiscal year. According to its Bureau of Medicine and Surgery, \$127,000 was appropriated for a study of the effectiveness of streptomycin on human tuberculosis in an investigation at the Naval Hospital in Corona, California. Other studies on streptomycin were already under way. Grants of \$9,300 for a study of minimal tuberculosis among low-income groups, \$26,700 for clinical and experimental research in thoracic surgery and pathology, and approximately \$25,000 for investigations in chemotherapy and tuberculosis and silico-tuberculosis represented further studies under sponsorship of the Navy. Additional grants included \$8,041 for an investigation of the biochemistry of chronic occupational disease, and \$7,000 for a cooperative research project concerned with the metabolism of the tubercle bacillus using carbon<sub>13</sub> as a tracer element.

As outlined above, the total tuberculosis research program reported by the Navy for the 1947-1948 fiscal year represents an allocation of \$203,041.

*Veterans Administration*

The Veterans Administration financed studies on the effect of streptomycin in tuberculosis in the amount of \$1,767,000 for 1947-1948, and 24 study units were included in the investigations (7, 8, 9). A study of the incidence of tuberculosis among student veterans, recommended by the Subcommittee on Tuberculosis of the National Research Council, which acts in an advisory capacity to the Veterans Administration in the establishment of studies aimed at improved medical care for veterans, was carried out at a midwest university at a cost of \$3,333.

Reported figures show a total allocation by the Veterans Administration of \$1,770,333 in 1947-1948 for tuberculosis research.

Thus, according to reports received, the cost of tuberculosis research within the Federal Government in the 1947-1948 fiscal year amounted to \$3,636,250. Of this figure, \$3,001,200 was the reported cost of research with streptomycin and other chemotherapeutic agents.

*State, County, and Municipal Health Departments*

At present, data on tuberculosis research in state, county, and municipal health departments are inadequate. Perhaps the deficiency can be explained by the fact that until the program of laboratory procedures is more clearly defined through the experimental studies of the Tuberculosis Control Division of the Public Health Service, and the present shortage of trained personnel has been overcome, establishment of research projects must lag.

An experimental program of BCG vaccination, sponsored by the Pennsylvania Department of Health, was reported at an approximate cost of \$10,000 for the period 1947-1948. This study is being carried out with federal funds as part of the grants-in-aid to states from the Public Health Service.

Additional research made possible by funds from official agencies included BCG studies at the University of Illinois, at a reported cost of \$40,000 to the Chicago Municipal Tuberculosis Sanitarium during the 1947-1948 period, and a study of the efficacy of streptomycin in the treatment of tuberculosis reported by the University of Pittsburgh and sponsored by the Pittsburgh Department of Health through a grant of \$72,000 during 1947-1948.

During 1947-1948, the New York State Department of Health, Division of Tuberculosis Control, carried out studies on the bacteriology and serology of tuberculosis, BCG production and administration, and improvement of culture media at an estimated reported expenditure of \$55,800 of state funds.

This brings the total contributions for tuberculosis research reported by official agencies to \$3,814,050, with \$3,073,200 devoted to studies of chemotherapeutic agents.

In the period covered by the survey, much clinical research was carried out in tuberculosis sanatoriums, general hospitals with tuberculosis departments, and other institutions for the care of patients with this disease. There are more than 800 such establishments in the United States, most of which are supported by federal, state, county, or city funds. During 1947-1948 several studies, including investigations of the effectiveness of chemotherapeutic agents in tuberculosis, were financed by grants, as indicated in the allocations of official agencies already mentioned or included in the following pages showing contributions by other groups. In addition, a sizeable amount of the cost of clinical research was absorbed in the cost of medical care. The latter cannot be estimated.

### *Voluntary Agencies*

#### *National Tuberculosis Association and its Affiliates*

Ever since the establishment of its Committee on Medical Research in 1920, the National Tuberculosis Association has continuously supported research studies in basic, background, and applied research with adaptation of research findings to experimental, demonstration, or clinical purposes (10). In proportion to its budgetary limitations, funds allocated for medical research have increased from \$500 in 1920 for a study of the anatomy of the lung by the late William Snow Miller, to \$95,550 in the fiscal year 1947-1948 for financing of 19 projects by qualified investigators. To the latter figure should be added approximately \$10,000 for administrative costs within the Association. During the fiscal year about \$40,000 was contributed by state and local tuberculosis associations for research studies recommended by the Committee on Medical Research and Therapy of the American Trudeau Society, Medical Section of the Association. In addition, some states sponsored research projects within their own borders and available figures indicate an expenditure of \$66,624, which includes \$28,533 for studies on chemotherapy. Of the \$40,000 mentioned above, \$15,000 (included in the figure of \$95,550) was appropriated for research with streptomycin in the treatment of tuberculosis. The remainder was set up as a reserve fund for inauguration of new projects and establishment of a fellowship program during the fiscal year 1948-1949.

Besides streptomycin research, the studies sponsored in the 1947-1948 fiscal year by the Committee on Medical Research and Therapy fell into three broad groups (1) clinical and epidemiological, (2) basic laboratory, and (3) laboratory programs of a special service type

In his report of May 17, 1948 (11) to the National Tuberculosis Association and its affiliates, Dr. Esmond R. Long, Director of Medical Research and Therapy, described the investigations as follows:

In the first group were noteworthy investigations of the course and prognosis of tuberculosis of minimal extent, particularly as it is observed in nurses, and studies on the prognosis of tuberculosis in children and its relation to the tuberculosis of adult life. Included in these studies were fundamental investigations on the significance of the tuberculin test and the differential diagnosis of minimal tuberculosis and other pulmonary diseases causing subacute and chronic pulmonary infiltrations with a radiological appearance like that of tuberculosis. Coordinated with this group were certain investigations on the effect of pregnancy on tuberculosis, and a study of the protective value of masks against infection with large doses of tubercle bacilli.

The basic laboratory studies included investigations long under way on the chemistry of the tubercle bacillus and the relation of specific fractions of the bacillus to the pathology and immunology of tuberculosis. Another group of studies included investigations on the enzyme systems concerned with the special type of tissue necrosis characteristic of tuberculosis, viz., caseation and the phenomenon of softening of caseous tissue and cavity formation. Other studies were concerned with the physiology and pathology of the lungs. Finally, investigations on mycology, stimulated by certain similarities of tuberculosis and histoplasmosis, broadened the scope of the laboratory investigations.

The service laboratory programs included (1) provision of a depot for standard strains of tubercle bacilli on which qualified investigators may draw to ensure comparability of their basic materials with those employed by other investigators, and (2) a group of studies designed to improve laboratory procedures in the diagnosis of tuberculosis to furnish standard techniques for inclusion in the "Diagnostic Standards" of the Association.

The budget of the National Tuberculosis Association for the fiscal year 1947-1948 also included \$32,505 for statistical and social research on tuberculosis. The studies were concerned with (1) continued compilation of state laws now in effect with regard to control of the disease, such as those having to do with the Means Test as a prerequisite for sanatorium care, disposition of the recalcitrant patient, case reporting methods, et cetera, (2) analysis of contact examinations, primarily household contacts, (3) further assistance in the establishment and use of central tuberculosis case registers in health departments throughout the country, (4) analysis of tuberculosis morbidity and mortality trends in the United States and foreign countries, (5) assistance to state and local tuberculosis associations in the promotion of statistical research, and (6) special studies as requested by various departments of the parent organization.

Allocation of funds for historical research for the fiscal year 1947-1948

amounted to \$5,571 for continued assemblage of important documents and recording the history of the National Tuberculosis Association

Thus, the total reported research program of the National Tuberculosis Association and its affiliates for the fiscal year 1947-1948 was \$210,250, with \$13,533 of this amount allocated to investigations with chemotherapeutic agents in tuberculosis

### *Foundations*

According to "American Foundations and Their Fields" (Sixth Survey (12)), there has been a rise in the number of foundations in the country from 23 in 1915 to about 600 in 1947-1948. The responsibilities and interests of these organizations are necessarily broad and varied, however, and a review indicated that probably only a small number were committed to medical research and, specifically, to research in tuberculosis.

Letters were sent to 23 foundations. Of these, three reported sponsorship of studies in tuberculosis research, 15 advised that for various reasons tuberculosis research was not included in their medical research programs for 1947-1948, and 5 did not reply.

The Commonwealth Fund reported an expenditure of \$48,075 for laboratory studies on constitutional factors in tuberculosis, investigations of chemotherapeutic agents, statistical and epidemiological research, and support of two fellowships. The John and Mary R. Markle Foundation contributed \$4,000 for nutritional studies in relation to tuberculosis and the Rockefeller Foundation allocated \$18,532 for an epidemiological study of the disease in Williamson County, Tennessee. It is probable that other broad investigations supported by these foundations, and not covered by these figures, included some tuberculosis research.

In correspondence with universities and others, it was learned that additional contributions for this group included \$8,500 by the Lillia Babbitt Hyde Foundation, \$12,000 by the Josiah Macy Foundation, \$2,400 by the Lessing J. Rosenwald Foundation, and \$2,500 by the Henry Oakes Foundation, the latter for studies in aluminum therapy of silicosis and the detection of early growth of tubercle bacilli.

Total support for tuberculosis research reported for 1947-1948 by this group, amounted to \$96,007.

Foundations with direct research programs include the Charles Cook Hastings Home, an endowed institution with a reported annual budget of \$81,550, of which \$47,711 has been estimated to be for research on nutrition in tuberculosis, the Mayo Foundation and Clinic, which estimated its annual expenditure at approximately \$50,000 for experimental and clinical research in tuberculosis antibacterial therapy, and the Edward L. Trudeau Foundation and the Colorado Foundation for Research in Tuberculosis, both of which are supported by funds from various sources.

The Trudeau Foundation, long established as a tuberculosis medical research center, was engaged in numerous projects in basic and applied research during

1947-1948 A large proportion of support for these investigations was derived from official and voluntary agencies, foundations, pharmaceutical houses and other industrial organizations, the cost of which is included in the appropriate group In addition, however, funds from private and other sources, as well as interest and dividends from the Foundation's endowment, were reported at approximately \$36,116

The Colorado Foundation reported an expenditure of \$13,619 for its 1947-1948 fiscal year, involving two investigations, viz, a study of antibiotics derived from *Fusaria* active against the tubercle bacillus, and a study of the metabolism of the tubercle bacillus Funds for support of these projects were derived from private sources and from the endowment fund of the Foundation

The National Jewish Hospital at Denver, a national, nonsectarian, tuberculosis medical center, with funds donated by private sources, mostly individual contributions, reported an expenditure of \$46,888 for tuberculosis research in its 1947-1948 fiscal year

Allocations for tuberculosis research during 1947-1948 as reported by the second group of foundations amounted to \$194,334, and the total reported by the two groups was \$290,341 Of this total, \$57,906 was designated as having been specifically allocated for studies on chemotherapy in tuberculosis

### *Manufacturing Firms*

Commercial organizations are contributing in large measure to the program of tuberculosis research This support is divided mainly into two groups, viz, pharmaceutical houses and firms manufacturing X-ray equipment The former group has done much to increase knowledge of the effectiveness of chemotherapeutic agents in the treatment of tuberculosis through studies under direct supervision and grants-in-aid to responsible investigators in universities and hospitals, while the latter group has promoted research within its own laboratories for improvement of machinery for the detection of tuberculosis

### *Pharmaceutical Houses*

In this survey, letters were sent to 10 pharmaceutical concerns Replies indicated that all were carrying on some research in tuberculosis Although the majority of the studies were concerned with chemotherapeutic agents, such as streptomycin, diasona, promizole, and subtilin, also included were investigations of the use of vitamins in tuberculosis therapy, the action of certain drugs following pneumonectomy and similar surgical procedures, and employment of the adrenal cortical hormone to overcome adrenal cortical insufficiency caused by tuberculous involvement of the adrenal gland

Eight experimental studies of the effect of streptomycin in the treatment of tuberculosis, sponsored by the American Trudeau Society (4, 5) were made possible by the contribution of more than \$1,000,000 worth of the drug by six commercial firms Results of these investigations are being published in book form by the National Tuberculosis Association This research was supported by

the Abbott Laboratories, Eli Lilly and Company, Merck and Company, Charles Pfizer and Company, E. R. Squibb and Sons, and The Upjohn Company.

Additional research with chemotherapeutic agents in tuberculosis, as well as with other drugs already mentioned, was supported by the six organizations named above and the four remaining commercial firms to which inquiry was directed, viz., Hoffman LaRoche, Inc., Parke, Davis and Company, Sharp and Dohme, and Wyeth Inc.

Because of their extensive and interrelated research programs, several manufacturers stated that the amount devoted exclusively to tuberculosis research was difficult to estimate and the reported figures are therefore incomplete. However, estimated contributions of the 10 pharmaceutical houses, based on replies received, amounted to \$1,881,675, of which about \$1,204,500 was spent for research with chemotherapeutic agents. The remainder, devoted to other studies in tuberculosis research, also included a small number of fellowships.

In reports from the foundations, it was learned that during 1947-1948 grants for chemotherapeutic research in tuberculosis were made by the Bristol Laboratories and the Eaton Laboratories amounting to \$4,400. This increases the total contributions from 12 pharmaceutical houses to \$1,886,075, and the amount for investigations with chemotherapeutic agents to \$1,208,900.

### *Other Industries*

Also in reports received from the foundations, it was found that other industries, principally light and heavy metal manufacturing and mining operations, contributed \$83,550 during the 1947-1948 period, of which it was stated 50 per cent could be designated for research on tuberculosis and silicosis.

### *Firms Manufacturing X-ray Equipment*

Between World War I and World War II, knowledge of the value of roentgenographic examination as a diagnostic procedure for tuberculosis was greatly increased and research was responsible for marked improvement in X-ray equipment, making possible extensive mass chest roentgenographic surveys of the civilian population. Also, screening at induction and separation centers in World War II was a routine practice in an effort to prevent induction of persons with this disease into the armed forces and to detect tuberculosis on discharge. Without continuous research on the part of the manufacturing firms, such programs could not have been undertaken.

In the present survey, letters were sent to 13 firms manufacturing X-ray equipment. Of these, 12 reported research programs and one did not reply. Reported contributions by this group, which might fairly be designated as for tuberculosis research during the 1947-1948 period, amounted to approximately \$276,250. The 12 firms which reported studies carried out in their laboratories were Anseo, George W. Borg Corporation, E. I. DuPont de Nemours and Company, Eastman Kodak Company, Fairchild Camera and Instrument Corporation, General Electric X-ray Corporation, Kelly-Koett Manufacturing Com-



pany, Machlett Laboratories, North American Philips Company, Powers X-ray Service, Standard X-ray Company, and Westinghouse Electric Corporation

### *Universities*

In considering the part played by the universities, it is necessary to state at the outset that this survey includes only the 70 medical schools designated at the time as approved by the American Medical Association (13). It is fair to assume that some research in tuberculosis is being carried out in other institutions and in the smaller colleges. Although it is not feasible to include research expenditures of such schools in this report, it is obvious that schools of public health, schools of public health nursing, and sociology departments of various colleges make expenditures for research bearing directly or indirectly on tuberculosis. It may be noted also that the American College Health Association, through its Committee on Tuberculosis, carries out an annual survey, in cooperation with the National Tuberculosis Association, of the extent of tuberculosis among college students. This might justifiably be termed tuberculosis research.

Replies to the 70 letters mailed to schools of medicine indicated tuberculosis research projects in 39. Of the remaining 31, 20 reported studies in prospect or expressed an interest, and 11 simply indicated that no tuberculosis research was carried out during the time specified in the inquiry.

In the period 1947-1948, grants to the 39 universities or institutions incorporated or affiliated with them, such as the Henry Phipps Institute in Philadelphia, amounted to approximately \$300,000. This support was derived from official and voluntary agencies, foundations, and manufacturing firms, and the sums have already been included appropriately in the foregoing pages. However, the universities *per se* make a substantial contribution of personnel, laboratory facilities, supplies, et cetera, to augment the grants in-aid of research received from outside sources. According to reported figures, an approximation of funds furnished by the universities during 1947-1948 was \$134,400. In addition, funds from private sources, mostly individuals, donated directly to the universities and allocated for tuberculosis research during the same period, were reported to be approximately \$57,000.

Thus, the total contribution of the 39 universities for tuberculosis research in 1947-1948 was \$191,400. This figure seems low, and represents only reported sums. Because the same laboratories may be used for research in other fields and personnel may be interested in several research projects, it is difficult to arrive at a true estimate; the total expenditure of the universities was probably much higher than is shown here.

### COMMENT

As has been indicated, support for tuberculosis research in the United States comes from the official agencies (mainly the federal group), voluntary agencies, foundations, manufacturing firms, and universities. The contributions of the five groups as calculated from their reports for a twelve-months' period during 1947-1948, and the proportion devoted to studies in chemotherapy of tuberculosis, are shown in table 1 and figures 1 and 2.

Reflected in the following figures is the interest in the last few years in streptomycin and other chemotherapeutic agents which have shown promise in the treatment of tuberculosis. The reported allocation for investigations in chemo-

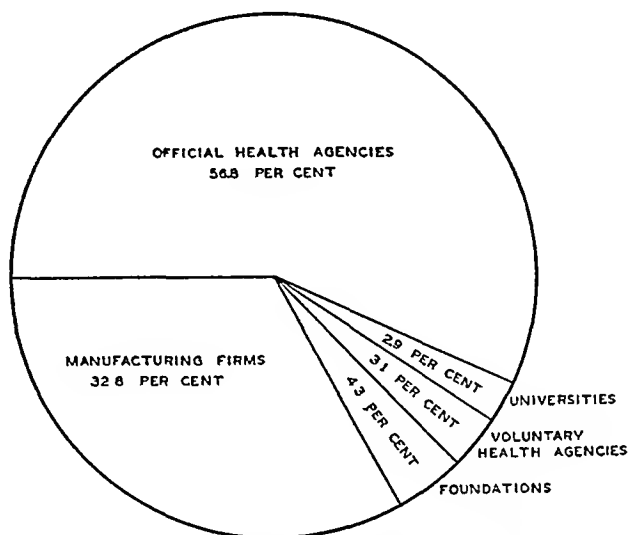


FIG 1 Total contributions to tuberculosis research, classified by contributing agency, 1947-1948

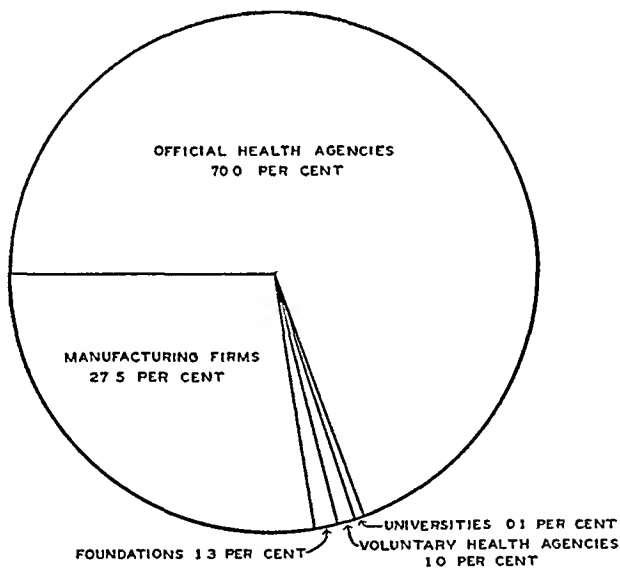


FIG 2 Cost of chemotherapy studies in tuberculosis, classified by contributing agency, 1947-1948

therapy of tuberculosis represents approximately two-thirds of the cost of the total tuberculosis research program in this country during a twelve-months' period in 1947-1948

Primarily, according to the survey, official agencies supported background, applied, and developmental research in tuberculosis. The National Tuberculosis Association, the voluntary agency, was engaged to a large extent in basic and developmental research, and a few projects of the same type were reportedly supported at the state and local level.

The foundations which furnished grants-in-aid sponsored studies in all four categories of research, governed, no doubt, by the types of requests received which seemed to indicate proposals promising addition to the knowledge of tuberculosis or furthering its control. The second group of foundations, *i.e.* those with direct research programs, were engaged largely in basic research studies, although background, applied, and developmental research projects formed a part of their work.

TABLE 1

*Total Allocations for Tuberculosis Research and Cost of Chemotherapy Studies in Tuberculosis, Classified by Contributing Agency, 1947-1948*

Calculated for a twelve-months' period

CONTRIBUTING AGENCY	TOTAL CONTRI- BUTIONS TO TUBERCULOSIS RESEARCH	COST OF CHEMO- THERAPY STUDIES IN TUBERCULOSIS
All agencies	\$6,710,141 00	\$4,388,039 00
Official health agencies	3,814,050 00	3,073,200 00
Manufacturing firms	2,204,100 00	1,208,900 00
Foundations	290,341 00	57,906 00
Voluntary health agencies	210,250 00	43,533 00
Universities	191,400 00	4,500 00*

\* Except for intangibles, chemotherapy studies in tuberculosis in universities are, in general, supported by grants from other agencies listed in the table.

The program of the manufacturing firms was concerned particularly with applied and developmental research but included also investigations in basic research.

The greatest contribution of the universities was their reservoir of personnel and laboratory facilities, the cost of which cannot be accurately reckoned. Potential expansion of basic research by inauguration of additional studies by qualified investigators, and through a program of graduate and undergraduate fellowships for promising young research workers, rests largely with this group in respect to personnel and facilities.

In conclusion, it must be stated that large sums were spent by official and voluntary agencies for tuberculosis case finding through mass chest roentgenographic surveys and health education of the public during the period covered by this report. In addition, much clinical research in tuberculosis was absorbed in the costs of medical care, to which individuals and many community health and welfare organizations contributed (14, 15). Although the importance of this phase of the program is well recognized, the amount of funds which could be designated for tuberculosis research is impossible to estimate.

*Acknowledgment*

Grateful acknowledgment is made to Miss Mary Dempsey, Statistician, National Tuberculosis Association, her staff, and to Miss Helen Goodell of the New York Hospital-Cornell University Medical College, for compilation and art work in table 1 and figures 1 and 2

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# THE RESECTED POSTTHORACOPLASTY LUNG<sup>1 2 3</sup>

## A Clinico-pathologic Correlation

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### INTRODUCTION

In the past two decades, thoracoplasty has become one of the safest and most effective measures for the treatment of pulmonary tuberculosis. During this time, the technique of performing the operation has improved. Moreover, increased experience has resulted in a better selection of patients on whom the procedure has been performed so that good clinical results are obtained in the majority of instances. Unfortunately, however, there is a sizeable percentage of patients receiving this treatment who continue to have either sputum positive for tubercle bacilli, persistence of cavity, or both. This group of patients constitutes the "thoracoplasty failure" as considered in this study.

The reasons for thoracoplasty failure are obviously of interest and of considerable importance. At times, one can surmise from the clinical evaluation why the treatment failed. In other cases, the autopsy findings may assist in answering the question (1). Neither of these approaches is entirely satisfactory, however, because they do not allow a clinico-pathologic correlation at the proper time. The autopsy findings in a patient dead from pulmonary tuberculosis are not the same as those in a living patient prior to the terminal phases of the disease.

Thoracoplasty failure can be treated by revision thoracoplasty, cavernostomy, or by pulmonary resection. In recent years, pulmonary resection has been used with increasing frequency and the lungs thus removed have allowed, for the first time, the opportunity to study the pathology of the disease in the living patient. It is hoped that the present clinico-pathologic study may further the understanding of the basic reasons for thoracoplasty failure and permit more rational selection of patients for thoracoplasty and resection.

### MATERIAL AND METHODS

During the years 1934-1948, inclusive, 323 pulmonary resections were performed for tuberculosis by the Overholt Thoracic Clinic. Thoracoplasty failure was the indication for resection in 64 instances. Since 2 of the 64 cases had various complications prior to the thoracoplasty (empyema, fistula, and previous

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<sup>2</sup>Presented before the Medical Section, as part of the symposium on *Surgery*, at the 45th annual meeting of the National Tuberculosis Association, Detroit, Michigan, May 5, 1949.

<sup>3</sup>The pathologic studies were made possible through a grant from the Committee on Medical Research and Therapy of the American Trudeau Society, Medical Section of the National Tuberculosis Association.

lobectomy), they were not included in the present study, which is based on a clinical and pathological evaluation of the remaining 62 cases

The pathological findings in each case have been reviewed and have included microscopic examination of multiple areas of the parenchyma as well as of the individual segmental and larger bronchi. Of prime interest in the pathologic review were (1) tabulation of important sites and types of active tuberculosis, (2) search for possible anatomic causes to explain the pathogenesis of the failure of collapse therapy. In only 4 instances was the pathological material not available for satisfactory review.

The clinical course of the 62 cases was likewise reviewed. Although follow-up observations were available for all of the cases, an adequate review of pre-resection roentgenograms was not possible in 8 instances. In the remaining 54 cases, the roentgenograms and clinical courses were reviewed with particular reference to type of disease and to apparent clinical causes of thoracoplasty failure.

Table 1 gives the general statistics for this group of patients and is self-explanatory. However, certain facts bear emphasis. There is one more resection than the number of patients because one patient had two lobectomies (pneumonectomy in 2 stages).<sup>4</sup> It should be noted that pneumonectomy was performed in 45 of the 62 patients because the distribution of disease in the thoracoplasty-failure group does not usually lend itself well to lobectomy. Only three segmental resections were performed in combination with lobectomy and these were done in preference to pneumonectomy only because of the poor reserve of the patient or very questionable contralateral disease.

The age of patients varied from 19 to 49 years. Over 50 per cent (33) were between 30 and 40 years. It is interesting that none was over 49 years of age, although a significant number of the entire resection series are above this age. There was a predominance of females, as is true with most series of resections.

The duration of illness varied from fifteen months to thirty years. Only 48 per cent had been ill for less than two years, 37 per cent had been ill for two to five years, 40 per cent from five to ten years, and 18 per cent over ten years. Thus, resection in this group represents surgical treatment predominantly in middle-aged patients with long-term illnesses. It is not surprising, then, that 44 of the 62 represent failures, not only of thoracoplasty, but of a combination of collapse therapy measures as listed in table 1. Only 18 patients had no pre-thoracoplasty collapse therapy. In addition, 14 had revision thoracoplasty, 4 cavernostomy, and pneumonectomy had been attempted elsewhere on one patient. There were 36 patients who had contralateral lesions which were considered either controlled or controllable in each instance.

Bronchoscopy was not performed in 7 patients. Of the remainder, 30 had negative findings on bronchoscopic examination and endobronchial tuberculosis was present in 23. Attention is called to the fact that 15 of these lesions were

<sup>4</sup>Right upper and middle lobectomy was first performed on this patient. Her sputum remained positive and the lower lobe was removed at the second operation. The cause of failure on pathological examination was ulceration of the middle lobe stump.

TABLE 1  
General Statistics  
Clinical and Pathological Evaluation of 62 Cases of Thoracoplasty Failure

<i>Total Number of Patients</i>			62
Males			21
Females			41
<i>Operations Performed</i>			63
Pneumonectomies			46
Right			21
Left			25
Lobectomies			17
R U L			5
R U and M			3
R U and Sup			
Div Rt			
L L			1
R U and M and			
Sup Div			
R L L			1
L U L			6
L U and Sup			
Div L L L			1
<i>Duration of Disease (15 months to 50 years)</i>			
1 to 2 years	3 (4.8 per cent)	} 42 per cent	
2 to 3 years	7		
3 to 4 years	11		
4 to 5 years	5		
5 to 10 years	25	} 40 per cent	
10 to 15 years	6	} 18 per cent	
15 to 20 years	4		
20 to 25 years	0		
30 years	1		
<i>Previous Therapy</i>			
A Ipsilateral Lung			
Pneumothorax			24
Phrenic			22
Pneumoperitoneum			3
Cavernostomy			4
Attempted pneumonectomy			1
Revision thoracoplasties			14
B Contralateral Lung			
Pneumothorax			6
<i>Contralateral Disease (36 of 62 Patients)</i>			
23 of 45 pneumonectomies			
13 of 17 lobectomies			
<i>Endobronchial Disease</i>			
Negative bronchoscopy			32
No bronchoscopy			7
Positive bronchoscopy			23
a submucosal	6		
b ulcerative	2		
c ulcerostenosis	6		
d fibrostenosis	9		

obstructive in type, 6 being ulcerostenosis and 9 fibrostenosis. Distribution of these obstructing bronchial lesions is similar to that reported in 1945 (2), with 47 per cent in the left main bronchus and 73 per cent of the total in the left main bronchus or right upper lobe orifice. No stenotic lesions were seen below the level of the superior division of the lower lobe. Only two lesions involved the trachea and these were extensions from the right main bronchus.

#### PATHOLOGY

In evaluating the pathology of the resected lung, the first consideration was given to a determination of the types and sites of active tuberculosis which were capable of producing sputum positive for tubercle bacilli. From such an analysis, the types of pathology readily fell under three headings (table 2) (a) active tuberculous cavity, (b) endobronchial tuberculosis, (c) extensive parenchymal tuberculosis. Many specimens had more than one type or site of major pathology, which accounts for a total greater than the number of specimens.

TABLE 2  
*Types of Tuberculous Disease*

Active tuberculous cavity		50
Multiple	5	
Lower lobe	9	
Endobronchial tuberculosis		40
Stenosis	7	
Bronchiectasis	10	
Extensive parenchymal tuberculosis		9

In many instances, there were scarred foci encountered which unquestionably represented healing or healed cavities, but these were not tabulated. In one specimen, an epithelial-lined cavity showing no evidence of active tuberculosis was found. This, likewise, was not included in the tabulation. There were 50 specimens which showed cavities and multiple cavities were present in 5 instances. While the commonest site for cavity was the apical posterior segment of the upper lobe, they were found elsewhere as well. The average size of the upper lobe cavities was 2 to 3 cm. in greatest diameter. The nine lower lobe cavities were notably larger, however, and, as a group, averaged several times the size of those found elsewhere.

Endobronchial tuberculosis was of three types: (a) stenosis (either hyperplastic or fibrous), (b) tuberculous bronchiectasis, (c) diffuse mucosal and submucosal disease (table 2). The endobronchial disease tabulated was arbitrarily limited to that involving segmental or larger bronchi and was proved to be tuberculous by microscopic examination. While diffuse tuberculosis of the mucosa and submucosa of one or more segmental bronchi was usually the only bronchial finding, in 10 cases there was an associated tuberculous bronchiectasis and in 7 specimens there was stenosis of the orifice of a large bronchus. The distri-



bution of the bronchial disease will be reported in a future study. It will be noted that the incidence of stenosis was not as high in the pathological specimen as was the incidence as determined by bronchoscopy. This is because the lung was at times resected through, or just distal to the stenotic area. A cavity was usually, but not always, present when there was endobronchial disease of any type. If a cavity was present, the disease of the bronchus was not necessarily limited to the segment or lobe containing the cavity.

Extensive parenchymal disease was a prominent pathologic feature in 9 specimens but was always associated with either cavity, endobronchial disease, or both.

The second item of pathologic interest was a determination of possible pathogenetic factors in the thoracoplasty failure. Items included under this heading were (a) thick, fibrous cavity wall, (b) thick, fibrous, or calcified pleura, (c) lower lobe cavity, and (d) severe endobronchial disease of the stenotic or bronchiectatic type (table 3).

The presence of a very thick, fibrous wall around a cavity obviously acts as a deterrent to the proper collapse which should be expected from thoracoplasty; such a factor was found in 5 specimens. Similarly, a markedly thickened or calcified pleura resists adequate collapse, and was considered to be an anatomic feature predisposing to failure in 7 instances. Fibrosis of the parenchyma itself was undoubtedly a factor in failure frequently but, since it was so difficult to evaluate from the examination of the pathology alone, it was not tabulated.

Extensive disease, with or without cavitation, is not listed as an anatomic reason since it may equally well represent a manifestation of failure. There is one exception to this, however. Cavities in the lower lobe (9 cases) were notably large and poorly collapsed as compared to those elsewhere in the lung. Such a finding was constant enough to warrant listing the location of a cavity in the lower lobe as a pathogenetic reason for thoracoplasty failure.

Endobronchial disease of the stenotic or bronchiectatic type was present in 17 specimens and in each was considered anatomically to be a predisposing factor to failure (figures 1, 2). This is particularly true when the endobronchial tuberculosis has become severe enough to be independent of its parent parenchymal focus (3).

In addition to the causes listed, there were many other conditions which may have played an anatomic, basic role in the pathogenesis of the thoracoplasty failure. It was apparent, however, that the complete evaluation and explanation of the causes of thoracoplasty failure cannot be made from the pathological specimen alone. In the majority of instances, a clinico-pathologic correlation is necessary.

#### CLINICAL CAUSES FOR THORACOPLASTY FAILURE

Table 4 records the clinical factors contributing to thoracoplasty failure in the 54 patients upon whom complete data, including prethoracoplasty and pre-resection roentgenograms, were available. The factors listed here are those commonly found in the literature (4). However, the term "tension cavity" has been

TABLE 3  
*Factors in Pathogenesis of Failure*

Thick cavity wall	5
Thick pleura	7
Lower lobe cavity	9
Endobronchial disease	17
Stenosis or bronchiectasis	

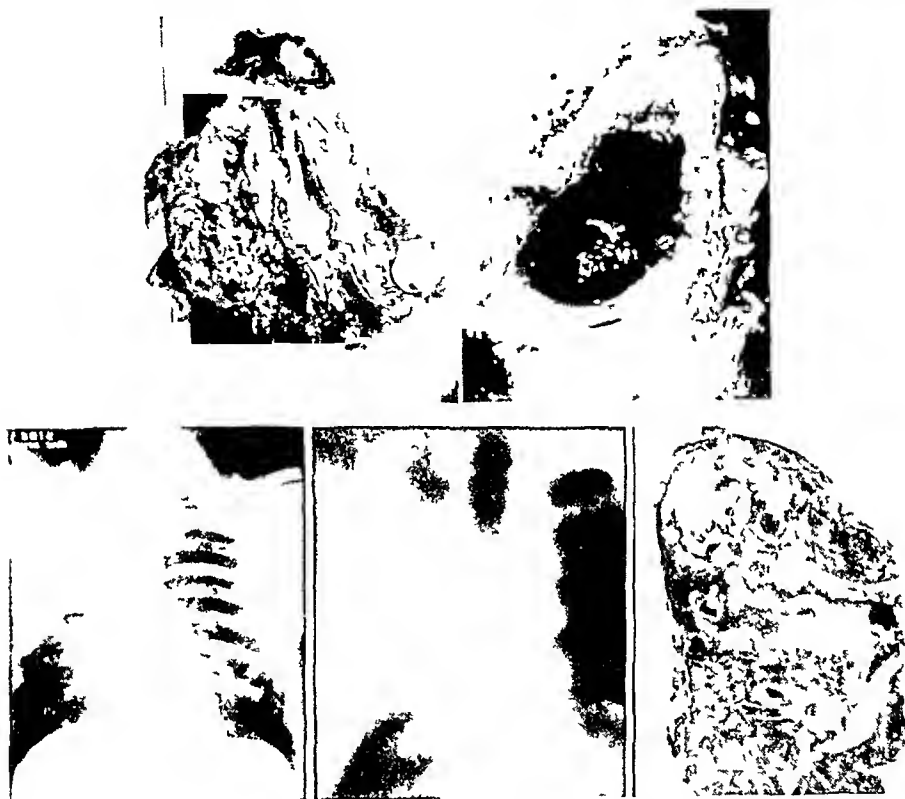


FIG 1 Bronchial disease and tuberculous bronchiectasis. Mr. F. H., age 49 (Upper left) Duration of disease 4 years prior to thoracoplasty and 12 years prior to resection, hyperplastic endobronchial stenosis of lobar bronchus with extensive bronchial involvement distally (Upper right) Enlargement of stenotic bronchus

FIG 2 Good thoracoplasty—residual cavity and extensive bronchial disease. Mr. W. G., age 27. Duration of disease 8 months prior to thoracoplasty and 20 months prior to resection. No endobronchial disease present bronchoscopically. (Lower left) A postthoracoplasty roentgenogram demonstrates adequate collapse. (Center) Laminogram reveals presence of cavity in collapsed area. (Lower right) Surgical specimen contains an upper lobe cavity (2.3 cm) and much endobronchial disease

intentionally avoided because of the difficulty in determining just when a cavity falls into this category.

Inadequate surgery was an outstanding feature in this group of patients (figure 3). Adequate collapse of the cavity-bearing area was obtained in only

11 instances. Totally inadequate collapse was present in 40 cases. The factors causing this failure of collapse are listed and are self-explanatory except that delayed stages were probably a more common cause than is indicated. One patient had a flaccid chest wall as the result of an extensive apicolectomy with failure of regeneration of ribs. Naturally, resection was the only therapy that could be offered this patient for her residual disease.

The size, number, and location of cavities were undoubtedly contributory causes of failure in many of the 40 patients. The 6 factors singly or in combination, were present in 36 cases. Predominantly exudative disease was present in 11 cases at the time of thoracoplasty. Spread of the disease to the base of the lung occurred in 4 and became one of the major causes of failure in these patients.

TABLE 4  
CLINICAL CAUSES OF THORACOPLASTY FAILURE  
(Percentage)

A. <i>Technical Factors</i>		
1	Transcero procedure not executed	40
2	Long anterior stumps	25
3	Inadequate number of ribs resected	11
4	Delayed stages	16
5	Failure of rib regeneration	1
B. <i>Factor Related to Tuberculous Disease</i>		
1	Characteristics of cavity	
a	Large cavity (4 to 6 cm.)	26
b	Great cavity (6 cm. +)	9
c	Multiple cavities	13
d	Unfavorable location	8
2	Exudative disease	11
3	Spread of disease to base	4
4	Endobronchial tuberculosis	21
C. <i>Mechanical Factors</i>		
1	Thickened pleura	9
2	Presence of pneumothorax	8
3	Bronchiectasis	3
D. <i>No Identical Clinical Cause of Failure</i>		4

(figure 4). Endobronchial disease was present in 21. It was submucosal in type in 6, ulcerative in 2, ulcerostenotic in 6, and fibrostenotic in 7.

The pleura was sufficiently thick in 9 cases to interfere with relaxation of the chest wall. Pneumothorax was present in 8 and displaced the cavity inferiorly and medially in each case. Bronchiectasis was clinically evident in 3.

In 4 patients no clinical cause of failure could be determined.

#### COMMENT

One factor that hampered the adequate analysis of the material was the difficulty in distinguishing pathologically between cause and effect of thoracoplasty failure. Since by definition a thoracoplasty failure is a case with sputum per-

sistently positive for tubercle bacilli, any active tuberculosis which might give rise to this state is, in this sense, the pathological cause of thoracoplasty failure. From examination of the pathological specimen alone, however, it is usually impossible to be sure whether any individual type of disease or lesion is the pathogenetic cause or merely the manifestation of failure.

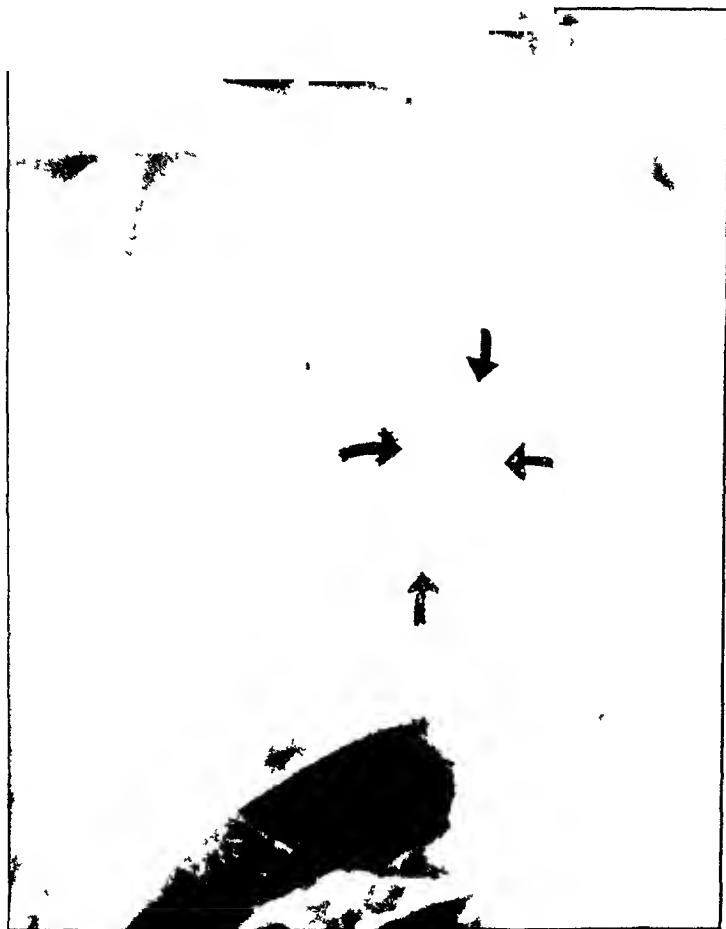


FIG. 3. Roentgenogram showing inadequate collapse. Mrs. A. D., age 46. Duration of disease 21 years prior to thoracoplasty and 30 years prior to resection. No endobronchial disease present. Roentgenogram demonstrates a poor thoracoplasty with resection of an inadequate number of ribs, presence of long anterior stumps, and posterior rib stumps with transverse processes. The cavity extends below the level of the highest unresected rib.

An additional point which made analysis and correlation more difficult was the fact that 40 of the entire group had an inadequate thoracoplasty from the surgical point of view. It is obviously unsatisfactory to study the pathology of thoracoplasty failure in a specimen if an adequate thoracoplasty has never been done.

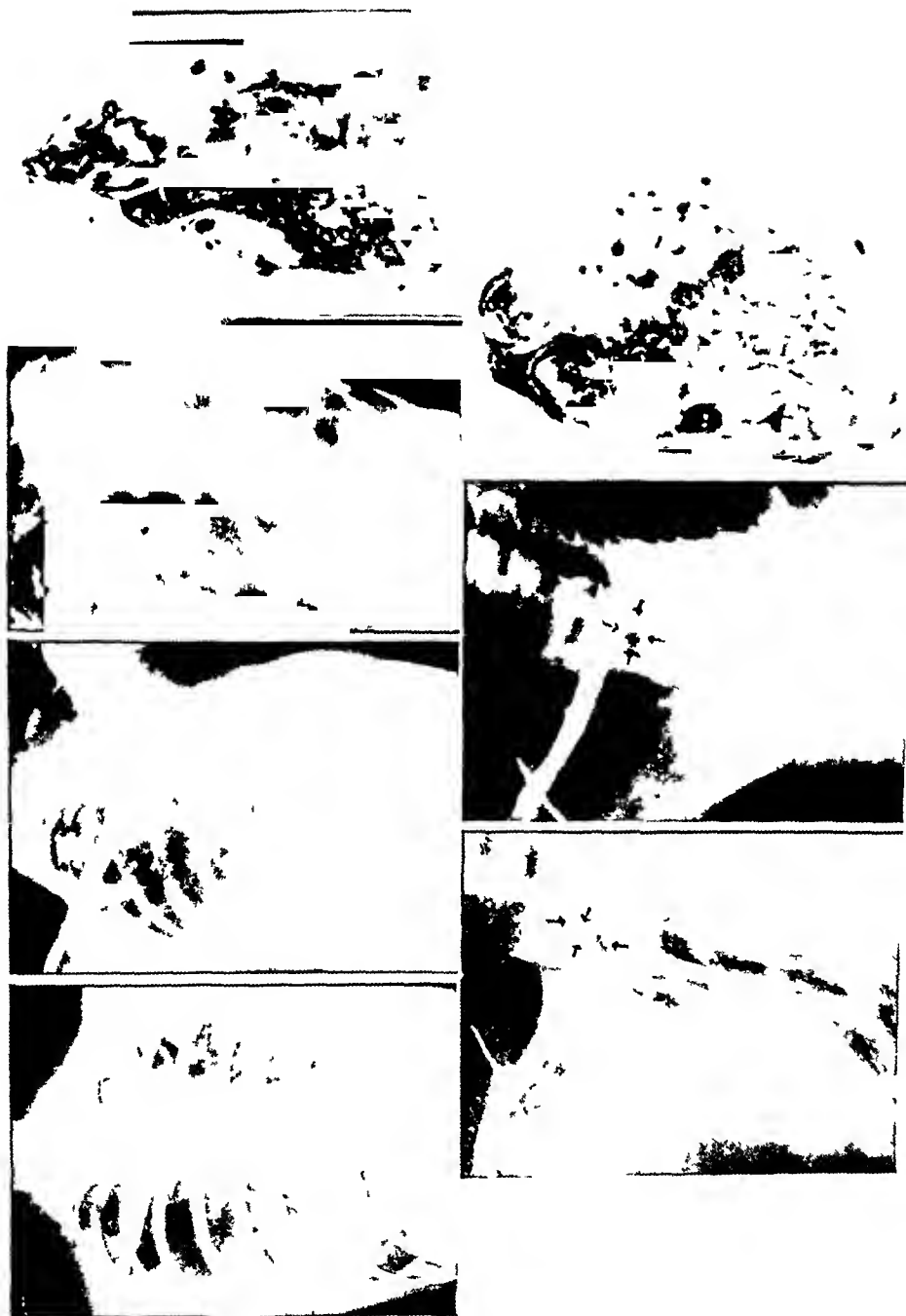


FIG. 1 (Top)  
FIG. 5 (Bottom)

The 14 cases who had a thoracoplasty which was considered technically and clinically adequate made up an interesting group. Only 4 of the group had initial cavities less than 4 cm in diameter. A review of postthoracoplasty roentgenograms and of the resected specimen revealed residual cavitation and inadequate cavity compression. These findings confirmed the impression that large and giant cavities, by their size alone, may predispose to failure of thoracoplasty even if it is adequately performed. Eleven of the 14 cases had exudative disease prior to thoracoplasty, often associated with a large cavity, some of which showed spread of disease and new cavity formation after thoracoplasty. Endobronchial disease was present by bronchoscopy in 5 cases prior to thoracoplasty. In the resected specimen, endobronchial disease was a prominent feature in 8. In 3 of the cases, no pathologic explanation for persistence of "positive" sputum was found, only a few small foci of submucosal tuberculosis being present in 2 and only extensive nontuberculous fibrosis and bronchiectasis in the third. In the final analysis of the 14 cases with adequate thoracoplasty, the features which stand out as the most probable causes of failure are large and giant cavities and exudative and endobronchial lesions, either of which may predispose to post-operative spread of disease.

In only 4 instances did the review of the charts and pre- and post-operative roentgenograms fail to show any cause for failure. These patients had satisfactory thoracoplasties with adequate collapse. Their cavities were under 4 cm and the type of disease should have usually responded to the treatment. None of them had endobronchial disease. Cavity was found in pathological examination in 2, one a residual cavity and the other a cavity that had developed in the inferior part of the left upper lobe as a result of an undetected spread of disease. In the other 2 instances, examination of the resected specimen revealed only a small amount of submucosal bronchial disease which was not considered to be an adequate explanation for the persistent discharge of tubercle bacilli in the sputum.

#### DISCUSSION

The 62 patients studied were from many parts of the country and their thoracoplasties represent the work of many surgeons, including our own group.

FIG 4 Failure because of spread of disease to base of lung. Mrs. D. P., age 38. Duration of disease 5 years prior to thoracoplasty and 18 years prior to resection. No endobronchial disease present bronchoscopically. (Upper left) Prethoracoplasty roentgenograms. Two large cavities (4.5 by 3 cm. and 4 by 3 cm.) in left upper lung field with a clear, left base. (Upper left middle) Spread to base following thoracoplasty. (Upper right middle) Oblique film demonstrates new cavity formation in area of "spread". (Upper right) Resected lung reveals the upper lobe disease controlled. Two cavities in lower lobe, and gross endobronchial tuberculosis of lower lobe bronchi.

FIG 5 Roentgenogram showing initial inadequate collapse, probably cause of later extension. Mrs. G. S., age 38. Duration of disease 9 years prior to thoracoplasty and 18 years prior to resection. A fibrostenosis of right main bronchus was present. (Lower left) Roentgenogram demonstrates inadequate thoracoplasty with long anterior stumps and cavity behind unresected transverse process. (Lower middle) The cavity persists after thoracoplasty has been revised when additional ribs resected but transverse processes left untouched. (Lower right) Surgical specimen presents a huge cavity, 10.5 by 3 cm. crossing the fissure line and bronchiectasis of the lower lobe.

Thus, they can be considered to reflect average concepts concerning case selection and what constitutes an adequate thoracoplasty. In this group, there can be no doubt that poor collapse as a result of a technically poor thoracoplasty was the outstanding cause of failure. Only the most complete thoracoplasty could possibly have controlled the majority of the lesions represented, but, in spite of this, transverse processes were not resected, long anterior stumps were left, and insufficient ribs resected in 40 of the 54 patients on whom adequate roentgenograms were available for study. In addition, in the 11 patients with obstructing lesions in the main bronchus, a complete thoracoplasty as recommended by

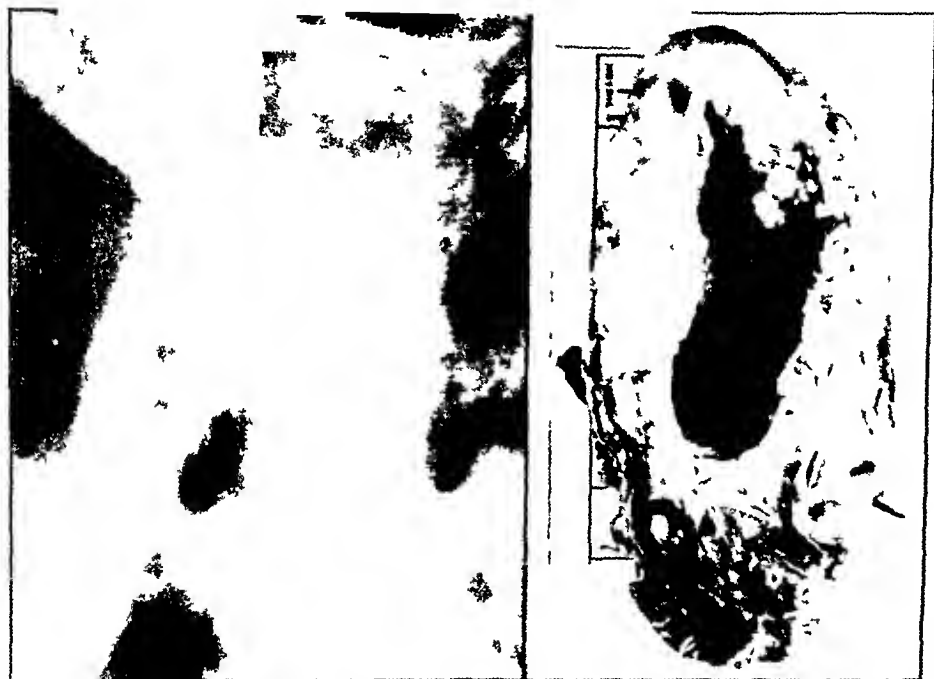


FIG. 6. Good thoracoplasty with persisting cavity, large, thick walled cavity with extensive emersion. Miss D. G., age 34. Duration of disease 2½ years prior to thoracoplasty and 4 years prior to resection. There was no endobronchial disease or bronchoscopy. (Left) Roentgenogram demonstrates persistence of cavity under a good technical thoracoplasty. (Right) Surgical specimen reveals 14.0 cm. cavity with thick walls and markedly thickened pleura.

Alexander (5) was not performed in a single case. A review of the roentgenograms revealed that a poor thoracoplasty was often the initiating factor of a long series of events that eventually led to the necessity of resection (figure 5).

An analysis of this group shows that they are patients predominantly of middle age with long-term illnesses. It is not surprising therefore that 44 of the total 62 represent failures, not only of thoracoplasty, but of a combination of collapse therapy measures as listed in table 1. Only 18 patients had no prethoracoplasty collapse therapy. The facts indicate that this group of patients was brought to pulmonary resection late and at a time when many of them were poor risks. It is our opinion that many cases in this series represented poor case selection.

for thoracoplasty and today could be treated more successfully by resection.

The third notable contributory cause to failure of thoracoplasty was a consequence of individual characteristics of the disease process (figure 6). Such characteristics include large and giant cavities which were so notable in the group with adequate thoracoplasty. An unfavorable position of the cavity in the lower lobe is another characteristic of apparent importance in that it cannot be properly compressed by thoracoplasty. Endobronchial tuberculosis, particularly when stenotic or bronchiectatic, as well as exudative disease, are likewise individual features of the disease process which seem to inhibit good results from thoracoplasty.

The fourth group of factors of importance are those of a mechanical nature which prevent adequate collapse and compression. Such features as thickened cavity wall, thick pleura, and the fibrotic indurated lung are examples of this group.

#### SUMMARY AND CONCLUSION

1. A clinico-pathological study of 62 instances of thoracoplasty failure in which pulmonary resection was performed is reported.

2. It is difficult, from the pathologic specimen alone, to distinguish between cause for failure and manifestation of failure. The best determination of cause can be made when the clinical findings are correlated with the pathology.

3. The outstanding contributory cause of failure was a technically inadequate thoracoplasty.

4. Poor case selection was a frequent contributory cause for failure.

5. Another reason for failure was a consequence of the individual characteristics of the disease process, such as bronchial involvement, exudative disease, large cavities, and distribution of disease.

6. Factors interfering with success of thoracoplasty also included features such as thick cavity wall, thick pleura, and a fibrotic, indurated lung, all of which interfere with collapse.

#### *Summary y Conclusiones*

##### *El Pulmon Postoracoplastico Resecado Correlacion Clinico-Patologica*

1. Este estudio clínico-patológico comprende 62 casos de fracasos de la toracoplastia en los que se ejecuto una resección pulmonar.

2. A base exclusiva del ejemplar patológico, resulta difícil distinguir la causa, de la manifestacion, del fracaso. La mejor determinacion de la causa es posible cuando se correlacionan los hallazgos clinicos con la patologia.

3. La más notable causa contribuyente del fracaso consistió en la insuficiencia técnica de la toracoplastia.

4. Una frecuente causa contribuyente al fracaso consistio en la mala seleccion de casos.

5. Otra causa del fracaso procedió de las características individuales del proceso patológico, es decir, invasion bronquial, forma exudativa de la enfermedad, tamaño de las cavinas y distribución de la dolencia.

6. El ultimo grupo de factores que impiden el éxito de la toracoplastia com-



piende puntos tales como espesor de las paredes de la cavema, espesamiento pleural, y fibrosis e mduracion del pulmon, todo lo cual obstaculiza el colapso

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### *Discussion of Paper by Doctor Meissner and His Associates*

*Dr Donald L Paulson, Dallas, Texas* In the surgical treatment of pulmonary tuberculosis we have a variety of procedures available to us today. Theoretically there should be no competition among these procedures. Each should be used in its proper place depending on the type of disease present and the condition of the patient, particularly from the standpoint of the patient's respiratory reserve. However, in practice it is not always possible to fit the appropriate procedure to the patient's individual needs. After a complete evaluation of his individual type of disease, various surgeons will employ a variety of procedures for the same type of disease. It is for this reason that studies such as Doctor Meissner and his associates have reported are of great value. One may not agree with the corrective procedures employed, but the reasons for failure are facts which we can accept. Perhaps these facts will bring us to more complete agreement on the type of procedure which is appropriate in a given case.

To illustrate this point, there can be no question that severe bronchial stenosis or bronchiectasis is better treated by resection. On the other hand in the absence of bronchial obstruction and severe bronchiectasis, and in the presence of a technically inadequate thoracoplasty (40 of 54 patients), particularly in the presence of contralateral disease (36 of 62 patients), I am sure that some of us would consider a revision thoracoplasty as the more appropriate procedure over resection. This may not be true in the presence of a large cavity considered uncollapsible. But even in this instance there are safer procedures available to us such as cricostomy, the use of extrapleural plombage, either by pack as used by Doctor Kinsella or lucite balls as suggested by Doctor Brewer.

Thoracoplasty for various reasons if properly performed is one of the safest and most effective measures which we have for the surgical treatment of tuberculosis. In cases in which there is an honest difference of opinion between the use of thoracoplasty or resection (excluding the bronchial strictures and bronchiectasis), we believe that the thoracoplasty should be done first. If an adequate thoracoplasty is effective, one has utilized a safer procedure. If it is not effective, one can then proceed to a resection on a more justifiable basis and, I believe, with less danger of contralateral reactivation of disease and a better functional result.

Doctor Wilson and I have discussed the necessity for more studies of this type. We are in agreement that these figures and the results should be broken down according to the indication for the surgical procedure. Although I realize that this fact was not rightfully included in this paper, I believe it is pertinent to the subject as a whole to know what the results of resection were in this group of patients reported here today.

# TUMORS OF THE MEDIASTINUM<sup>1</sup>

A Discussion of Diagnostic Procedure and Surgical Treatment Based on  
Experience with Forty-four Operated Cases

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## INTRODUCTION

Primary tumors of the mediastinum have ceased to be medical curiosities discovered principally at the autopsy table. They are now being diagnosed in increasing numbers by clinical examination. This is a result of greater interest in thoracic diseases in general, the routine employment of the chest roentgenogram as a part of the chest examination, and the use of mass roentgenographic surveys for the detection of pulmonary tuberculosis. Thus, the problem of what plan of action should be taken on the discovery of a possible mediastinal tumor is becoming more important to all physicians treating thoracic diseases. Should these lesions be disregarded because of the paucity of symptoms or is operation indicated in every case? Actually the writers believe there is a definite series of investigative procedures which, if carried out in each case, will determine in most instances whether or not a mediastinal tumor is present. This presentation is concerned with a review of these various diagnostic procedures and the therapy employed in the management of a large series of mediastinal tumors, 44 of which were treated by operation.

## INCIDENCE.

It is impossible to estimate the true incidence of mediastinal tumors, due to the fact that they are often diagnosed as other conditions. Primary neoplasms of the mediastinum are rare and the series reported have not been large. Heuer (1) in presenting seven years experience with tumors of the mediastinum at the New York Hospital recorded operations on 39 primary benign tumors, 17 malignant ones. In addition, 47 were classified as primary malignant tumors of the lymph nodes of the Hodgkin's lymphosarcoma group. Bradford, *et al* (2) reported 35 cysts and tumors of the mediastinum in 1946. Blades (3) presented the combined experience of the Army Thoracic Surgery Centers in the United States during World War II. He collected 94 benign tumors and 15 malignant ones which had been subjected to surgery, 94 of the 109 cases were detected by routine roentgen examination of the chest. Our operative experience consists of 44 primary tumors of the mediastinum of which 35 were benign and 9 malignant. We have treated a greater number of malignant tumors of the mediastinum which were not considered candidates for surgery.

Little attention has been paid to the occurrence of mediastinal tumors in mass

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radiographic surveys of the chest Prows (4) reviewed 2,821 twenty-one millimeter chest films taken as a mass survey on routine admission at a private hospital, the California Lutheran Hospital in Los Angeles, California The results are seen in table 1 It is of interest that the incidence of suspected mediastinal tumors was equal to that of suspected pulmonary tuberculosis, 2.26 per cent of positive findings, or 0.1 per cent of the entire survey This does not represent a true incidence of primary mediastinal tumor as many of these patients had screening chest roentgenograms or fluoroscopy before being admitted to the hospital It does point out, however, that more attention should be paid to the mediastinum in routine roentgenographic surveys of the chest

#### ANATOMY OF THE MEDIASTINUM

Figures 1 and 2 illustrate the anatomy of the right and left aspects of the mediastinum Pressure on the various structures depicted in the drawings accounts for the various symptoms, signs, and abnormal findings of the specialized diagnostic procedures discussed later on in this presentation

TABLE 1  
*Mass Chest Roentgenographic Survey of Routine Admissions  
California Lutheran Hospital (Prows)*

Cases examined roentgenographically	2,821
Cases with positive findings, all types	177
Cases with probable pulmonary tuberculosis	5
Cases with probable mediastinal tumors	5

#### SYMPTOMS AND SIGNS

For a considerable period of time in the growth of a mediastinal tumor no symptoms may be produced It is only when a "sensitive" structure in the mediastinum is pressed upon that these tumors make themselves known to the patient Thus, a mediastinal tumor may cause considerable compression of the lung away from the hilum without causing discomfort, provided a branch bronchus is not occluded It is not surprising that mediastinal tumors may sometimes grow to a considerable size without causing much difficulty to the patient Once this fact is well understood the clinician will not be surprised to have the presence of these tumors discovered by a routine or survey chest roentgenogram

The symptoms produced by a mediastinal tumor may be classified according to the disturbance in function of the various organs in the mediastinum The severity of symptoms depends upon the size and location of the tumor, the rapidity of growth, and the presence or absence of actual invasion of those organs Five main groups of symptoms may be recognized (1) neurological, (2) respiratory, (3) gastro-intestinal, (4) vascular, and (5) miscellaneous

*Neurological* Probably one of the earliest and most constant symptoms of tumors of the mediastinum is the feeling of a vague intrathoracic discomfort, fullness, or ache This is common in the tumors that press on portions of the

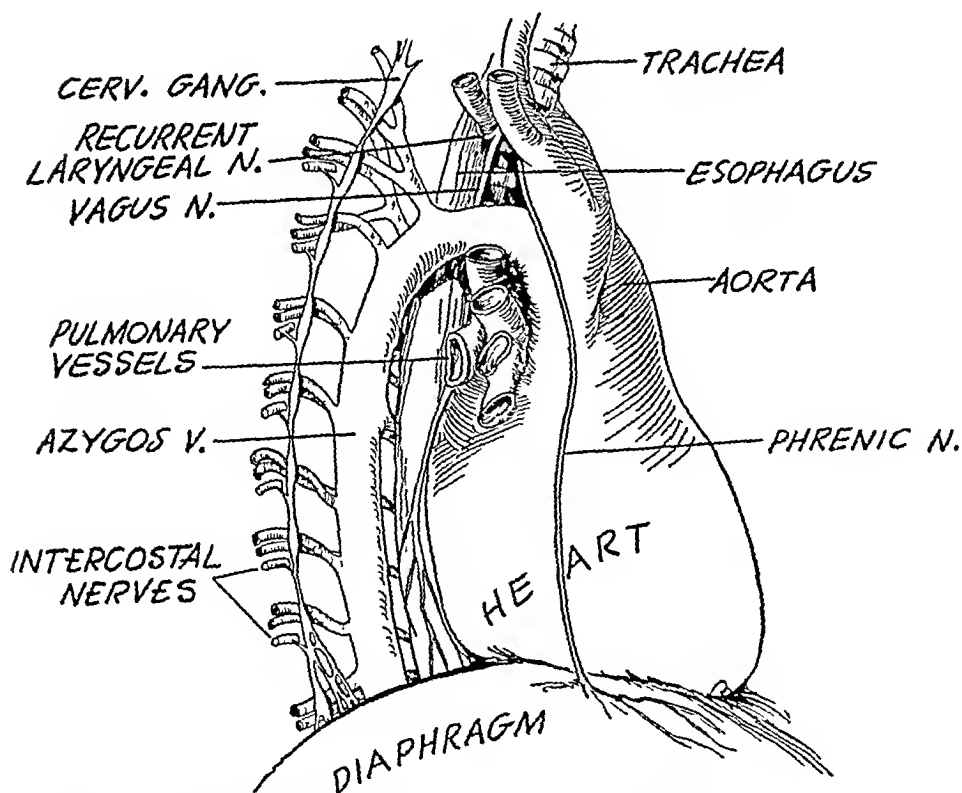
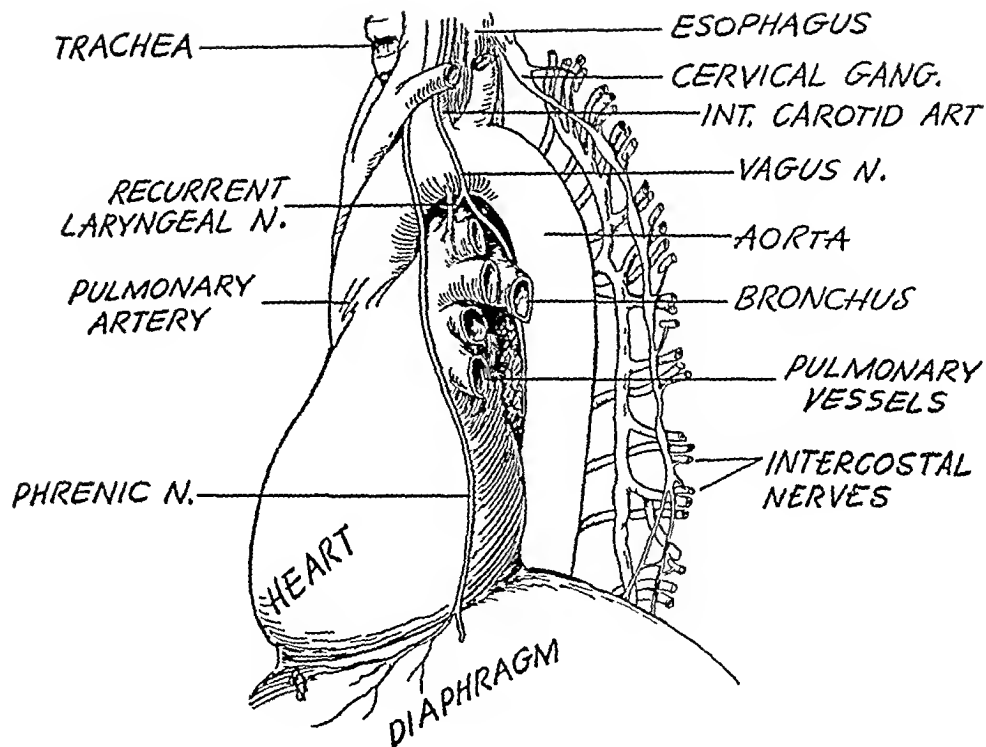


FIG 1 (Upper) Drawing of anatomy of left view of mediastinum

FIG 2 (Lower) Drawing of anatomy of right view of mediastinum

chest wall and so affect the sensitive intercostal nerves. Intercostal pain is a common finding in tumors of neurogenic origin, varying from a slight twinge of pain to a severe neuralgia. The pain may be pleuritic in character, being aggravated by respiration. With involvement of the cardiac nerves, an anginal type of pain may be produced. In fact, several of our patients had been treated for a number of years for angina pectoris and had their activities markedly curtailed because of this diagnosis. Erosion of the vertebra produces a boring type of interscapular pain which is very severe. Invasion of the brachial plexus causes severe pain in the upper extremities. "Dumbbell tumors" of the spinal cord and mediastinum may exhibit symptoms and signs of spinal cord pressure.

Other neurological symptoms include hoarseness due to paralysis of the recurrent laryngeal nerve from pressure on this structure. Hiccups may be present as a result of phrenic nerve stimulation, although this is rare. The finding of Horner's syndrome (myosis, enophthalmos, and ptosis of the eyelid) will point to involvement of the cervical sympathetics. Vomiting may result from vagal nerve stimulation although this is usually a result of other factors.

*Respiratory* Respiratory symptoms are the next most important group of symptoms which are the direct result of pressure of the tumor mass on some portion of the respiratory tract. Dry cough is usually noticed first, followed by the expectoration of sputum. The sputum is first mucoid but may become purulent, if obstruction to a bronchus exists and secondary infection supervenes. Pressure on a main bronchus or trachea results in wheezing, not unlike bronchial asthma. This is distinguished by the fact that it is often unilateral and is heard best on inspiration. Pressure over the trachea results in a coarse rhonchus and stridor. The brassy cough may also be the result of recurrent laryngeal paralysis. Dyspnea, which is mild at first, increases with increase in the size of the tumor and resultant decrease in vital capacity. Shortness of breath may occur with sudden onset, as with lobar pneumonitis, with no premonitory symptoms. Tumor may be suspected only when roentgenographic examination reveals a persistent shadow following subsidence of the pneumonia. Hemoptysis occurs in 20 per cent (5) of all mediastinal tumors. The hemoptysis results from the erosion of a blood vessel in the respiratory tract or secondary infection. Hemoptysis, secondary to a tumor of the mediastinum, is the fourth most common cause of pulmonary hemorrhage, being superseded in frequency only by tuberculosis, bronchogenic carcinoma, and bronchiectasis (5). Dyspnea is a prominent symptom of most mediastinal tumors of any magnitude.

*Gastrointestinal* Gastro-intestinal symptoms result primarily from pressure on the esophagus. Thus, difficulty in swallowing and a sensation of "sticking of food" in the gullet are the symptoms most commonly observed. The esophagus may be displaced considerably and only moderate obstruction result, provided there is no interference with the esophageal peristaltic waves. The occurrence of dysphagia is a serious symptom, which may mean carcinoma of the esophagus, and so is an indication for immediate and thorough investigation of the cause. Regurgitation of food occurs when the obstruction is nearly complete. Vomiting, however, is usually a symptom of advanced mediastinal malignancy and is not often seen in the benign cases.

*Vascular* Obstruction of the great vessels in the mediastinum, although rarely observed in benign tumors of the mediastinum, is a common finding in malignant mediastinal tumors. This symptom represents a poor prognostic sign. In the superior mediastinum, the veins are compressed first and show dilatation on exercise or bending over. As the obstruction of the superior vena cava progresses, cyanosis of the head and neck occurs with associated pounding in the head, headache, and tinnitus. Marked dilatation of the veins, edema of the head and neck and extremities represent advanced venous obstruction. The development of collateral circulation in the chest wall parallels the venous obstruction. Pressure on the inferior vena cava is less common. When this vein is obstructed, edema of the legs and ascites develop. Progressive venous obstruction due to a mediastinal tumor almost always means a malignant tumor. Occasionally, an inflammatory lesion may produce a venous obstruction, but these cases are rare.

*Miscellaneous* Fever is usually not a symptom of mediastinal tumor unless there is secondary infection in the lung due to pressure occlusion of the tracheobronchial tree. It is present in advanced malignancies, in some instances due to the breakdown of the tumor. The loss of weight and strength, secondary anemia, are evidence of advanced malignancies, but are less common than with malignant tumors found elsewhere in the body because of earlier deaths from compression of vital mediastinal organs. Marked loss of weight is usually secondary to esophageal obstruction. It is surprising how large benign mediastinal tumors may get without producing marked symptomatology.

#### PHYSICAL EXAMINATION

Early in the course of development of a mediastinal tumor there are few demonstrable physical signs. On palpation, tracheal deviation may be noted. Horner's syndrome and unilateral flushing point to involvement of the cervical sympathetic nerves. On percussion, the anterior or posterior mediastinum may be widened. The changes noted on auscultation in most instances depend upon the amount of obstruction to the trachea or bronchi present. Tenderness of the chest wall may be noted over the tumor. The development of herpes zoster would suggest the existence of intercostal neuritis from pressure on the affected nerve. In most advanced cases the signs of vascular obstructions are very spectacular. The distended neck veins, cyanosis and swelling of the neck, and dilatation of the capillaries on the chest wall usually point to the mediastinal obstruction of an extensive malignancy.

#### DIAGNOSTIC PROCEDURES

*Roentgen examination* The roentgen examination is the most important diagnostic aid for the identification of mediastinal tumor. In addition to the conventional postero-anterior view, lateral and oblique films show the location on the anterior posterior plane. Fluoroscopy and roentgen kymography are useful in distinguishing between the transmitted pulsation and the intrinsic expansile pulsation found in aneurysms of the great vessels. In the case of an aneurysm with rigid walls, however, or one filled with laminated clot, no pulsation may be noted. Body section radiography (planograms, tomograms, laminograms, et

cetera) both in the postero-anterior and lateral planes often tells the exact point of attachment of the growths and then effect on adjacent organs. If no expansile pulsation is present in the aneurysm, the distinguishing of an aneurysm from a mediastinal tumor may be extremely difficult. Seldom, indeed, does an aortic aneurysm develop in a person in whom all serologic tests for syphilis are negative. The injection of 70 per cent diodrast into the median or cephalic vein will frequently reveal the presence of the suspected aneurysm. In some instances, to show the arch and the descending portions of the aorta, a retrograde carotid injection must be made. This technique clearly outlines the arch and descending aorta and is most helpful when aneurysms of the arch or of the descending aorta are suspected. In posteriorly located tumors, barium study of the esophagus shows possible changes in the esophagus effected by the tumor. Similarly, bronchograms will demonstrate any bronchial distortion resultant from pressure of a mediastinal neoplasm.

*Endoscopy* Bronchoscopy is an important diagnostic procedure when the suspected mediastinal tumor is in such a position as to press upon the trachea or major bronchi. By endoscopic examination the amount, if any, of external compression on the trachea or bronchus, or occlusion from a neoplasm within these organs, can be accurately determined. The mobility and presence of inflammation of the bronchial walls will be accurately observed. The most important role of bronchoscopy, however, is the identification or exclusion of the primary bronchogenic carcinoma. This most common intrathoracic neoplasm may simulate tumor of the mediastinum. Early radical removal of bronchogenic carcinoma has proved the only successful cure. Thus, bronchoscopy always should be performed when bronchogenic carcinoma is a possibility. It should be emphasized that bronchoscopy is not indicated in all cases of tumors of the mediastinum. In posteriorly located tumors, those near the anterior chest wall, and those adjacent to the diaphragm, bronchoscopy is not necessary.

Esophagoscopy is indicated only in posteriorly located tumors where there is a possibility of esophageal involvement with the tumor. A carefully performed barium esophagram should be done first. No esophagoscopy should be performed unless there is definite evidence of changes in the contour of the esophageal shadow. In this instance too, carcinoma of the esophagus is the most serious condition to be discovered. The obstruction symptoms are usually paramount, however, and point to pathologic changes in the esophagus long before a mass or shadow is visible on the plain chest roentgenogram.

*Diagnostic pneumothorax* Diagnostic pneumothorax was popular a decade ago to distinguish between intra- and extrapulmonary tumors. It was used not only as a diagnostic measure but also to collapse the lung preparatory to performing a lobectomy or pneumonectomy. Actually the preliminary pneumothorax prior to lung resection has been found of minimal value. The diagnostic worth of the pneumothorax is limited in the presence of intrapleural adhesions and often fails to point out the site of origin of the tumor. The more accurate procedure is the exploratory thoracotomy, which is to be preferred to diagnostic pneumothorax. In rare instances diagnostic pneumothorax may be employed. With a pneumo-

thorax established, thoracoscopic examination may be helpful in arriving at a diagnosis. The frequently restricted manipulation of the thorascope, however, and the presence of a small pneumothorax pocket make this procedure of limited value. At the best it is greatly inferior to surgical exploration.

*Aspiration of tumor cells.* The recovery of tumor cells by means of a needle introduced through the intact chest wall is warranted occasionally. Only when there is a question of the presence of localized pleural fluid or when a tumor, if malignant, is obviously inoperable, is aspiration justified. It should not be used when the tumor is located anteriorly for fear of tearing one of the great vessels. In tumors located posteriorly or laterally located tumors of great size, aspiration may be employed. We do not believe that it is justified to aspirate a tumor preoperatively in a case where operation is clearly indicated solely to determine the cell type. One of our cases with a huge teratoid tumor of the mediastinum was treated as a case of tuberculous empyema. Finally the aspiration of hair by thoracentesis showed a dermoid to be present.

*Tests for specific granuloma.* The exclusion of aneurysm of the aorta is probably one of the most important points in differential diagnosis of tumors in the vicinity of the aorta. The performance of serologic tests for syphilis on specimens of blood or cerebrospinal fluid is an important diagnostic procedure not to be omitted. Tuberculin tests and examination of the sputum for tubercle bacilli should be employed if tuberculosis is suspected. Tests for coccidioides and coccinococcus disease and other specific granulations also may be of value.

*Trial X-ray therapy.* One of the most helpful diagnostic tests is the use of deep X-ray therapy in possible cases of Hodgkin's disease and the lymphoma-lymphosarcoma group. The prompt shrinkage of an anteriorly placed perihilar or hilar mass after the administration of a skin dose of from 750 to 1,000 r usually means a tumor of this group. This test represents a satisfactory diagnostic procedure because no other intrathoracic lesion is so radiosensitive. Furthermore, since no benign lesion is radiosensitive, the decrease in size of the tumor, as seen on the roentgenogram following this therapy, represents a contraindication to operation. Prolonged and extensive deep X-ray treatment should be discontinued if there has been no shrinkage in the size of the tumor after three or four weeks. Prolonged roentgen therapy will not only be ineffectual but also it may make the surgical removal of a benign tumor very difficult. If a mediastinal lesion primarily held to be malignant does not definitely decrease in size following radiation therapy, the patient should be explored at once.

*Biopsy.* Biopsy of accessible peripheral lymph nodes is always in order in any part of the body where the diagnosis of metastatic malignancy in lymph nodes is suspected. Mediastinal tumors present no exception to the rule. For the finding of malignant metastasis contraindicates surgical exploration.

*Surgical exploration.* This procedure is often the only certain means of establishing the diagnosis of a benign mediastinal tumor. If, after a careful analysis of the various tests outlined above, the diagnosis is in question, surgical exploration is indicated, provided the patient is a suitable subject for surgery. A more complete discussion of exploratory thoracotomy is presented later.



Comparison of symptoms of benign and malignant mediastinal tumors and certain differences between benign and malignant tumors is outlined in table 2

The malignant tumors produce local and constitutional symptoms which are invariably progressive. It is only when the benign tumors become very large or press upon "sensitive" organs that comparable symptoms are noted. Obstruction of the great vessels and the rapid development of collateral circulation on the chest wall is almost invariably a sign of a malignant lesion of the mediastinum.

#### LOCATION OF VARIOUS TUMORS

It is impossible to catalogue the location of all of the types of mediastinal tumors because of the lack of accumulated evidence on the rarer types and the differences of opinion regarding tumor location in the literature. This difference of opinion undoubtedly is based upon varied sites of origin for these neoplasms.

TABLE 2  
*Comparison of the Symptoms of Benign and Malignant Mediastinal Tumors*

BENIGN	MALIGNANT
1 Slow growth	Rapid growth
2 Usually unilateral	Often bilateral
3 Few constitutional symptoms	Marked constitutional symptoms
4 No pleural effusion	Pleural effusion frequent
5 Superior vena cava obstruction rare	Superior vena cava obstruction frequent
6 Peripheral nodes not enlarged	Peripheral nodes enlarged
7 Nerve paralysis rare	Nerve paralysis frequent
8 Pulmonary tissue compressed	Pulmonary tissue invaded
9 Border smooth and circumscribed	Border frequently irregular
10 No response to X-ray therapy	Lymphoid tumors respond

Nevertheless, it is worth while to point out the more usual location of the commoner types of mediastinal neoplasms as diagrammed in figure 3. It will be noted that neurogenic tumors, esophageal and gastroenteric cysts occupy a posterior location although the latter may present in the middle mediastinum. Bronchogenic cysts, although attached centrally, may present in either an anterior or posterior position. Lymphoid tumors involving the lymph nodes, such as the lymphoma, Hodgkin's, lymphosarcoma group are commonly found comparatively early in their development in an anterior or central position. Metastatic malignancies, teratoid tumors, thymic tumors, intrathoracic goiter, pericardial cysts, and possibly lipoid tumors develop in an anterior location. This leaves a very large group of rarer types of mediastinal tumors for which greater experience will be needed in order that they may be accurately located. It is true also that exceptions to the locations of the various tumors shown in figure 3 may be found. Nevertheless, it is believed that this diagram will be helpful in the majority of the cases in locating the types of neoplasms depicted in the diagram.

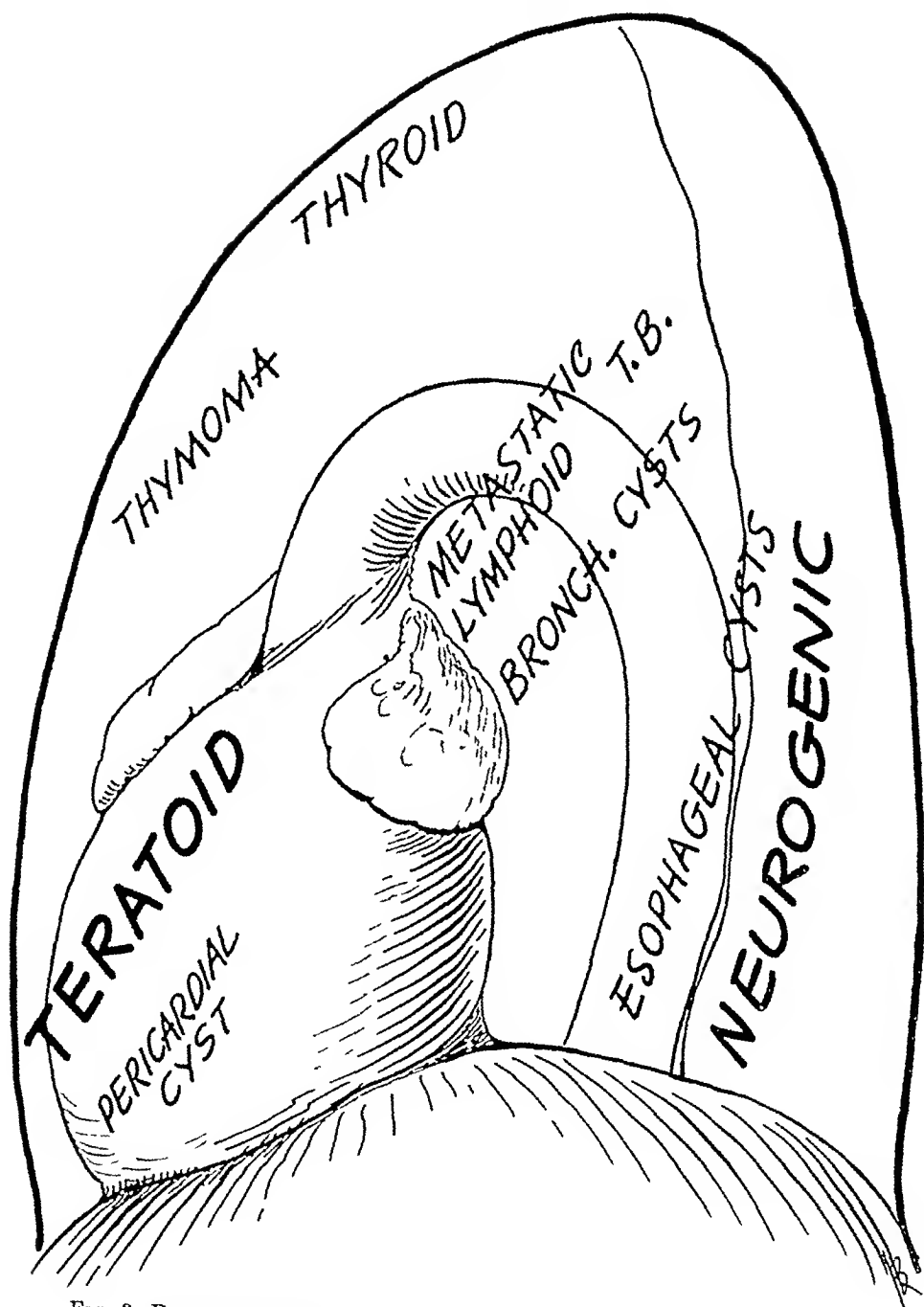


FIG 3 Diagrams of usual locations of common tumors of the mediastinum

#### DIFFERENTIAL DIAGNOSIS

A list of conditions commonly confused with mediastinal tumors is presented in table 3. Bronchogenic carcinoma is the most common intrathoracic tumor. It

is resistant to X-ray therapy, and surgical excision before spread has occurred is necessary to effect a cure. It is most important to distinguish this bronchogenic carcinoma from mediastinal tumor. In carcinoma of the lung arising close to the hilum, the shadow is usually irregular at the periphery. Bronchoscopy is frequently positive and the cancer cells may be found in the sputum. Cough, expectoration, and blood spitting are more common. However, in the superior sulcus tumor, now known to be a form of bronchogenic carcinoma in the great majority of cases, pain in the shoulder or arm, Horner's syndrome, and slight cough are present. It is extremely difficult to distinguish this lesion from a superior mediastinal tumor. If the tumor mass presents a smooth outline, it is likely to be a *benign mediastinal tumor*, and operation is indicated. If the borders are irregular, however, or there is evidence of invasion of adjacent tissues, we should suspect either a superior sulcus bronchogenic carcinoma or a malignant mediastinal tumor, both of which are usually inoperable by the time the diagnosis is made. If the presence of carcinoma of the lung cannot be excluded in

TABLE 3  
*Conditions which Simulate Mediastinal Tumors*

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1	Carcinoma of lung
2	Benign tumors of lung
3	Cysts of lung
4	Aneurysms of heart and great vessels (dissecting aneurysms)
5	Chest wall tumors
6	Tuberculosis of mediastinal lymph nodes
7	Hydatid disease
8	Mediastinal abscess
9	Thrombosis of superior vena cava
10	Diaphragmatic hernia

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the differential diagnosis of a possible mediastinal tumor, and no evidence of spread of the cancer can be found, surgical exploration is definitely indicated provided the condition of the patient permits this procedure.

Benign tumors of the lung occurring close to the hilum, if they occlude a major bronchus, usually produce atelectasis of the lung before they reach sufficient size to present a mediastinal mass on roentgen examination. They are readily diagnosed at bronchoscopy. If the main or branch bronchus is not occluded, however, it may be very difficult to distinguish between the two conditions. In most instances bronchial adenomas close to the hilum can be seen at bronchoscopy. Pulmonary cysts located close to the hilum, if filled with fluid, are indistinguishable from benign tumor of the mediastinum. Since operation is indicated for both of these lesions, the failure to distinguish between these conditions is not serious. Chest wall tumors located close to the sternum or spine often present a palpable mass. They frequently cause pain, but little, if any, pulmonary symptoms. Plainograms are helpful in showing their point of origin. Since they are potentially malignant, excision at the thoracic wall is indicated.

Aneurysms of the heart and great vessels present a difficult problem in differ-

ential diagnosis. Until the various surgical methods to treat aneurysms are perfected thoracotomy for aneurysms is not indicated. When the mediastinal mass shows expansile pulsation and the Wassermann test is positive, a syphilitic aneurysm is the most likely diagnosis. However, a nonpulsile aneurysm or one with a laminated clot may only be diagnosed by the contrast arteriography with injection of diodrast. In some instances aneurysm will be only diagnosed at exploratory thoracotomy. Dissecting aneurysms are particularly difficult to diagnose as they increase in size and cause pain similar to an invasive mediastinal tumor.

Thrombosis of the superior vena cava is a very rare condition. It is manifested by the signs of superior vena cava obstruction without the finding of enlargement of the mediastinum suggestive of a tumor on roentgen examination.

Enlarged mediastinal lymph nodes due to pulmonary tuberculosis usually contain calcium deposits. The tuberculin test is positive and there may be signs of healed pulmonary tuberculosis on the chest roentgenogram. Only occasionally will there be confusion with mediastinal tumors. The location and calcification of these nodes is usually diagnostic. They are mainly asymptomatic and should be left alone. A few have been removed according to certain reports of the medical literature; however, there is a weak indication for their excision.

Hydatid disease is not common in the United States and only when it is present in the lung adjacent to the mediastinum will mediastinal tumor be simulated. The precipitin test and skin tests are positive in high titers with an active hydatid cyst. Often hooklets may be recovered from the sputum.

Mediastinal abscess, though presenting a widening of the mediastinal shadow on roentgen examination, will rarely be confused with neoplasm of the mediastinum. Usually there is history of trauma, foreign body in esophagus, instrumentation, et cetera. High fever, tachycardia, dyspnea, great weakness, and prostration usually come on rapidly. Thus the signs and symptoms of an acute infection are paramount. The development of a fluid level in the mediastinum is diagnostic of a mediastinal abscess. Intensive antibiotic therapy and prompt surgical drainage are indicated.

Diaphragmatic hernia is usually diagnosed by a careful upper gastro-intestinal roentgen study. However, if the herniated sac contains only omentum and not a portion of the stomach or intestines, then a tumor of the mediastinum will be simulated. We have operated upon two such cases in our series.

#### TYPES OF MEDIASTINAL TUMORS

In table 1 are recorded the various types of mediastinal tumors found in our series. Neutrogenic tumors were most common, while teratoid tumors were second and cysts third in frequency. Blades (3) also found primary nerve tumors most frequent, with bronchogenic cysts second, teratoid tumors third, and pericardial cysts fourth. These groups of mediastinal tumors make up three-fourths of the benign tumors that are subjected to surgery. A miscellaneous group is included in the remainder. The malignant mediastinal tumors operated upon are few in

number and so varied in type as to prevent cataloging. The salient characteristics of the most common benign mediastinal tumors are presented.

TABLE 4  
*Types of Mediastinal Tumors in Writers' Series*

BENIGN		MALIGNANT	
Neurogenic tumors	16	Sarcoma	5
Teratoid tumors	8	(a) Spindle cell	2
Cysts	5	(b) Fibroblastic	1
(a) Bronchogenic	3	(c) Lipo	1
(b) Pericardial	2	(d) Neuro	1
Thymoma	2	Hodgkin's	3
Thyroid	2	Endothelioma	1
Leiomyoma	1		
Cystic hygroma	1		
Totals	35		9



FIGS. 4 and 5. Neurofibroma of posterior mediastinum. A 23-year-old secretary had a chest film taken as part of a mass survey for pulmonary tuberculosis at the state fair. Tumor mass discovered.

FIG. 4 (Left). Posterior-anterior view of chest shows sharply circumscribed ovoid soft tissue mass behind cardiac shadow.

FIG. 5 (Right). Lateral projection demonstrates tumor to be posteriorly next to spine. After film was taken, patient admitted she had some left chest pain. Benign neurofibroma removed at thoracotomy performed through posterolateral approach. Patient now well.

**Neurogenic tumors.** Primary nerve tumors represent one of the three most common types of mediastinal tumors and are the most important growths of the posterior mediastinum. Neurofibroma, neuroblastoma, ganglioneuroma,

et cetera may be found. In 1910 Heuer and Andrus (6) collected 108 cases of these tumors and in 1911 Heuer, Kent, *et al* (7) reviewed 105 collected cases, including 18 from Barnes Hospital. Most neurogenic tumors are relatively asymptomatic. Dull intercostal pain, not regarded as being important by the patient, is usually the first early symptom.

Several of the cases in our series were discovered quite accidentally in persons who considered themselves to be well but who, on further questioning, admitted



FIGS. 6 and 7. Teratoid tumor of anterior mediastinum. A 55-year-old engineer complained of cough, dyspnea, and pain in right anterior chest of twenty years' duration. X-ray therapy given fifteen years previously without relief.

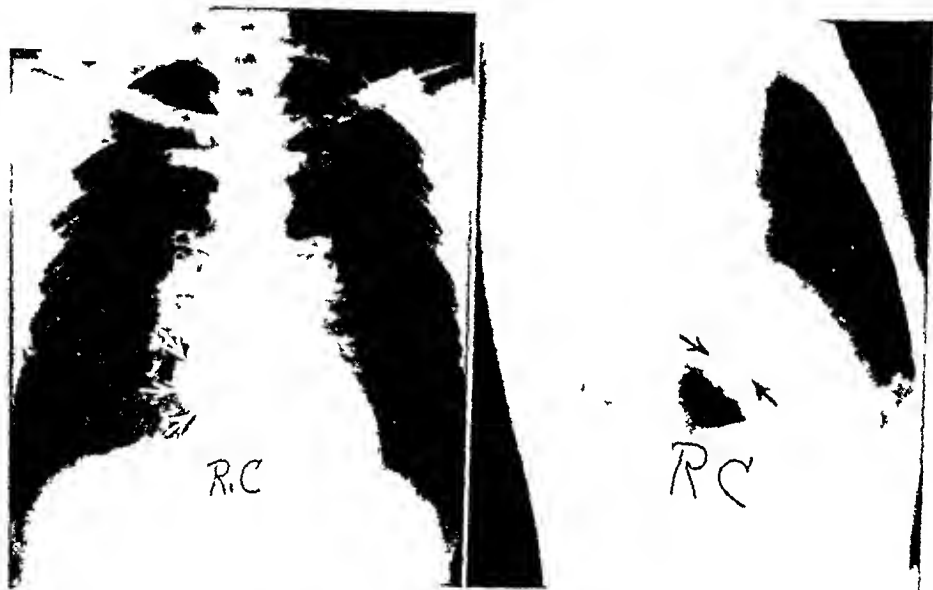
FIG. 6 (Left). A round sharply circumscribed homogenous mass, as dense as the cardiac shadow, is seen protruding from the right mediastinum, resting on the diaphragm on the posterior inferior film.

FIG. 7 (Right). Lateral view reveals this rounded mass to have an anterior location. A benign teratoma of the anterior mediastinum was removed by a thoracotomy performed through the posterolateral approach. Patient is now well and working.

slight chest pain. Horner's syndrome in one case proved to be evidence of a neuroganglioma, although the various types of nerve tumors cannot be distinguished clinically. When clinical signs and symptoms of moment are noted, most often malignant changes have taken place. This occurs in 37 per cent of the cases (7). Roentgen examination shows a characteristic shadow, smooth in outline, which may be lobulated and is of moderate soft tissue density, sharply circumscribed in the posterior mediastinum (figures 4 and 5). A careful search for erosion of the vertebrae should be made for this is strongly suggestive of intra-spinal extension of the tumor in a dumb-bell-like configuration. Neurogenic

tumors do lend themselves to surgical removal in the benign state. Since approximately one-third of them become malignant, they should be removed as soon as diagnosed, even though asymptomatic.

**Teratoid tumors** The group of teratoid tumors includes both the dermoids and teratomas, of which the latter are most common according to Harrington (8). Teratoid tumors are the most frequent benign neoplasms of the anterior mediastinum, 251 cases having been collected (9). These tumors grow slowly and



FIGS. 8 and 9. Bronchogenic cyst of mediastinum. A 36-year-old male accountant complained of hemoptysis and a "tumor in the lungs." Patient had known rheumatic heart disease, completely compensated. Bronchoscopy showed some distortion of the right lower lobe bronchus.

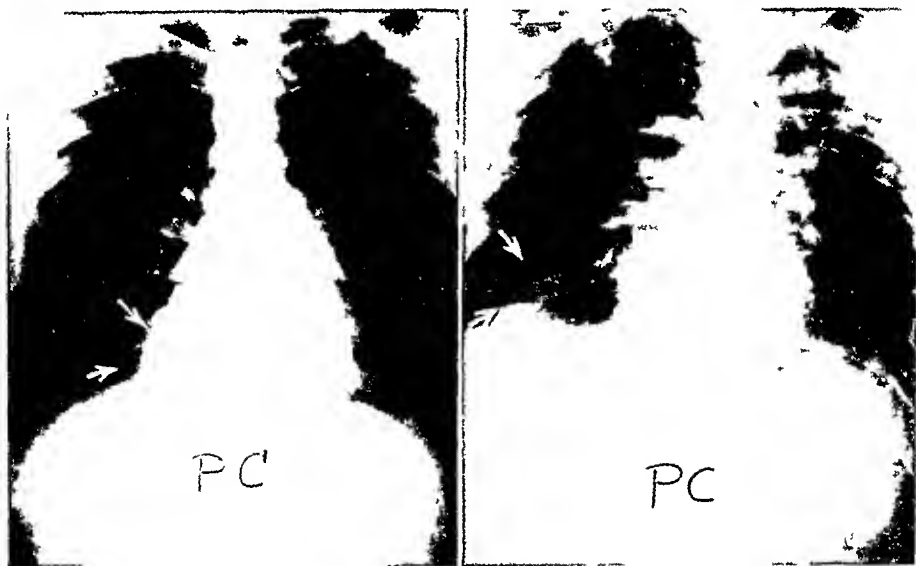
FIG. 8 (Left) Small circumscribed mass projecting from the lower right mediastinum is seen on posterior anterior film.

FIG. 9 (Right) A sharply circumscribed mass of central mediastinum is partially obscured by the cardiac shadow. Preoperative diagnosis: either adenoma of bronchus or mediastinal tumor. A benign bronchogenic cyst of the mediastinum was removed. Postoperative course uneventful. It is questionable whether this cyst was responsible for hemoptysis.

usually present symptoms before puberty. Intermittent cough, respiratory infections, and thoracic pain are the common symptoms. It may be coughed up when erosion has occurred in the bronchial tree, or it may be aspirated by a needle introduced through the chest wall. In some instances the tumors may have a cervical extension. Roentgenologic examination shows a dense, smooth, round tumor usually in the anterior mediastinum, occasionally an irregular border is seen (figures 6 and 7). Several cases have been reported in the posterior mediastinum. If teeth or bone are present, there is no question about the diagnosis. Teratoid tumors have been found to be malignant, 12.9 per cent of the cases (9). Once malignant change has taken place and invasion of structures contiguous

to the tumor has developed, the chance of cure by any method of treatment is exceedingly remote. Surgery of the benign teratoid tumors has been very successful, while X-ray therapy has shown little beneficial effect. It is obvious, therefore, that early surgical removal is urgently indicated.

*Bronchogenic cysts* Cysts of bronchogenic origin are uncommon. Blades (3) found 35 cases in the literature up to 1946 and added 23 additional cases in his collected series from Army medical centers. Bronchogenic cysts may arise from any point along the tracheobronchial tree and be present in either the anterior or posterior mediastinum. Cough and substernal discomfort are the usual complaints.



FIGS 10 and 11 Pericardial cyst. A 44-year-old dentist complained of pain in the right anterior chest for several years.

FIG 10 (Left) The posterior-anterior chest film demonstrated an oval homogenous shadow blending with the cardiac silhouette at the level of the diaphragm.

FIG 11 (Right) Oblique film reveals shadow to be anterolateral in location, extending outward from the cardiac outline. A pericardial cyst was removed by thoracotomy performed through a posterolateral approach. Patient is well and free of symptoms.

and the signs of infection may be present. In most instances the cysts are entirely asymptomatic and are discovered only on routine chest films. On the roentgen examination they appear as rounded or oval masses often in either the anterior or posterior mediastinum (figures 8 and 9). The shadow may be ill-defined on the lateral view. Fluoroscopy often reveals movement of the mass on swallowing, due to the attachment to the trachea for upper mediastinal cysts. These cysts are insensitive to X-ray therapy. If infected, there is no question about their removal. If asymptomatic, their removal is necessary because of the difficulty in distinguishing these lesions from teratoid tumors and bronchogenic carcinoma, where excision is definitely indicated.

*Pericardial cysts* Cysts of the pericardium have been reported in the literature in only 21 cases. Though usually asymptomatic, slight anterior chest pain



was noted in the 2 cases in our series. These cysts present in the anterior mediastinum as circular or oval masses which are less dense than teratoid tumors, and on fluoroscopy are definitely attached to the pericardium (figures 10 and 11). Roentgen therapy is ineffectual in reducing the size of the cyst. The true diagnosis can only be made by exploratory thoracotomy, at which time the removal is technically a simple procedure. Operative intervention is indicated, therefore, to rule out more serious types of mediastinal and pulmonary tumors for which surgery is the only hope.



FIGS 12 and 13. Thymoma. A 55 year old rancher had increased cough, expectoration, and dyspnea for several years.

FIG 12 (Left) Posterior anterior film of the chest shows a slightly lobulated homogeneous mass extruding out from the left lateral border of the heart.

FIG 13 (Right) On the lateral projections a lobulated shadow is present in the anterior mediastinum overlying but distinct from the heart shadow. Bronchoscopy showed displacement of left main bronchus. Pemeillin therapy given for three weeks before operation because of chronic bronchitis. A large thymoma of the anterior mediastinum was removed through the posterolateral approach. Patient is much improved and now working. Residual cough is present probably on basis of low grade bronchiectasis secondary to prolonged bronchial obstruction from the benign mediastinal tumor.

*Thymus.* The vast majority of thymic tumors are malignant, several hundred having been reported in the literature (10). We are excluding those thymic tumors found in association with myasthenia gravis for this latter disease so dominates the clinical picture as to present problems not pertinent to this discussion. It seems worthwhile, however, to comment on the two benign cases in our series. Both had substernal distress and cough as predominating symptoms. More often benign thymomas are asymptomatic. Roentgen examination reveals a mass in the anterior mediastinum in the region of the thymus which is fairly dense, but exhibits no particular characteristics (figures 12 and 13). It cannot

be distinguished from lymphoid tumor of the mediastinum. If X-ray therapy is ineffectual, removal is indicated since the great majority of thymic tumors undergo malignant degeneration.

*Miscellaneous benign tumors* The other benign tumors in our group of cases included thyroid, leiomyoma of the esophagus, and cystic hygroma. We have not encountered such rare neoplasms as gastro-enteric cysts, hemangiomas, fibromas, xanthomas, et cetera. The reader is referred to the excellent recent collective review of the literature compiled by Thompson (11) in 1947 as well as the earlier reports of Heuer and Andrus (8), Bradford, *et al* (2), Blades (3), and others.

#### MALIGNANT TUMORS

Only 9 malignant neoplasms were operated upon in this series. In at least four times that number of cases we were able to make this diagnosis of malignant mediastinal tumor without operation, so that no surgery was done. In 5 instances some type of sarcoma was found, in 3 cases Hodgkin's disease was the diagnosis, while the final case was proved to be an endothelioma. No one of these cases was cured by surgery as it was impossible to remove completely these malignant tumors because of invasion of vital structures.

#### INDICATIONS FOR SURGICAL OPERATIONS

It is now generally agreed that all benign mediastinal tumors should be removed by surgery (1, 2, 3, 6, 11, 12). This plan of treatment is based on the fact that benign mediastinal tumors are potentially malignant. To remove them when they are present as discrete circumscribed tumors is to take advantage of a golden opportunity to cure the patient. In waiting until marked symptoms are present, the one chance to effect a cure may be permanently lost. Furthermore, some benign mediastinal tumors may become so large as to seriously interfere with pulmonary and cardiac function, with continued growth, death supervenes even though no actual malignant change has taken place. The surgical excision of benign mediastinal tumors when severe cardiopulmonary symptoms have developed is often difficult and the results less certain. In some instances pulmonary tissue has been compressed and destroyed by secondary infection, so that lobectomy or pneumonectomy must be performed as well. The risk of operation for early cases is very small and should be less than 3 per cent with qualified anesthetists and surgeons. The chances of cure are practically 100 per cent when a discrete benign mediastinal tumor can be removed completely.

On the other hand, surgery is not indicated for most malignant mediastinal tumors. Rarely a malignant tumor may be removed before extensive metastasis has occurred. As has been stated, tumors of the lymphoma group uniformly respond to deep X-ray therapy. With experience the roentgenologist and the surgeon will be able to tell in most instances which cases should have a test dose of roentgen therapy. We do not now advocate, by any means, the routine use of X-ray therapy in all cases of mediastinal tumor, although we formerly held this

view (12) However, if there is no response to the X-ray treatment in three or four weeks' time, then surgery should be promptly undertaken To prolong the roentgen treatments after an adequate test dose has been administered results in no benefit to the patient The removal of a benign lesion will be rendered more difficult and hazardous and the result, therefore, less certain When there is not definite evidence of a malignant neoplasm of the mediastinum and X-ray therapy has failed, surgical exploration is then indicated

#### SURGICAL TREATMENT

Our early cases were operated upon without the benefit of antibiotics However, the last 22 patients in this series received penicillin routinely on the day before surgery and for one week thereafter In several instances the presence of severe chronic bronchitis necessitated a longer preoperative administration of the drug No postoperative pulmonary or pleural complications were seen with the use of penicillin We prefer the posterolateral approach to the mediastinum to the anterior one, because a much better exposure of the pleural cavity is gained by this approach Splitting of the sternum is feasible when an antero-superior mediastinal tumor presents directly beneath the sternum in some instances Endotracheal anesthesia is necessary Most benign tumors of the mediastinum can be shelled out if one locates the proper plane of dissection The operative technique must be meticulous with due regard for the important structures in the mediastinum The large veins must be handled with great care, for they are easily torn in the dissection This is especially true if considerable roentgen therapy has been employed Because the blood supply of a mediastinal tumor is often great, care must be taken to identify the vascular trunks supplying the tumor, particularly aberrant arteries arising from the great vessels Temporary water seal, catheter drainage, is employed for twenty-four to forty-eight hours The usual postoperative precautions for any thoracotomy are employed to prevent postoperative pulmonary complications The course after surgery is mild and usually the lung expands rapidly Most of the patients may be discharged in one week to ten days

#### RESULTS

No deaths occurred in this series of operated cases in which the cause of death could be attributed to the operation In one patient death occurred two months after operation due to a spontaneous rupture of the esophagus in a case where a benign neurofibroma had caused necrosis of the esophageal wall In a case of cystic hygroma extruding down from the neck to the mediastinum, the cell type was benign It was impossible to remove the tumor completely All other cases of benign mediastinal tumors were cured by the operation In the malignant cases, recurrence of the tumor was the rule although several patients have been alive for several years following surgery The prognosis of these patients is still poor

#### SUMMARY AND CONCLUSIONS

Many mediastinal tumors are now being discovered by routine roentgen films of the chest A definite plan of investigation has been presented for patients with

possible tumors of the mediastinum. This is based upon a proper evaluation of symptoms, physical signs, and specialized procedures. The specialized procedures consist of various roentgen studies (including the use of planograms and contrast media), endoscopy, test for specific granuloma, trial X-ray therapy, biopsy of accessible lymph nodes, and surgical exploration. By means of this plan of investigation it is possible to differentiate between benign and malignant mediastinal tumors and other intrathoracic lesions in most instances. The clinical and roentgen findings of the common types of benign mediastinal tumors has been discussed.

Since all benign mediastinal tumors are potentially malignant and X-ray therapy is ineffectual, surgical removal is definitely indicated. The golden opportunity for removal of a mediastinal tumor is presented when the lesion is discrete and the symptoms are absent or minimal.

X-ray therapy is effectual only for lymphoid tumors. In all other malignant tumors the chance of cure is very poor. Therefore, it is the responsibility of every physician to urge that the relatively asymptomatic benign mediastinal tumor be removed before malignant change develops. The risk of operation is slight and the percentage of cures is high.

#### SUMARIO

#### *Tumores del Mediastino. Discusion del Procedimiento Diagnostico y del Tratamiento Quirurgico a Base de lo Observado en Cuarenta y Cuatro Casos Operados*

Hoy día se descubren muchos tumores mediastínicos por medio de las radiografías corrientes del tórax. Para los enfermos en que existe tal posibilidad, preséntase un plan bien definido de investigación, basado en la justipreciación de los síntomas, signos físicos y procedimientos especializados. Los últimos comprenden varios estudios roentgenológicos (incluso empleo de planografías y medios de contraste), endoscopia, ensayo para granuloma específico, roentgenoterapia tentativa, biopsia de los ganglios linfáticos accesibles y exploración quirúrgica. Por medio de este plan de investigación, es posible diferenciar, en la mayoría de los casos, los tumores benignos y malignos del mediastino y otras lesiones intratorácicas. Discútense los hallazgos clínicos y radiológicos en las formas más comunes de los tumores benignos del mediastino.

Visto que todos los tumores mediastínicos benignos son potencialmente malignos y que los rayos X resultan ineficaces, la extirpación quirúrgica está netamente indicada. El momento óptimo para la excisión de un tumor del mediastino es cuando la lesión es discreta y no hay síntomas o éstos son mínimos.

Los rayos X sólo surten efecto en los linfomas. En todas las demás neoplasias malignas, bien pocas son las probabilidades de curación, por lo cual, a todos los médicos les corresponde la obligación de encauzar la extirpación de todo tumor mediastínico benigno y relativamente asintomático antes de aparecer alteraciones malignas. El riesgo que entraña la operación es leve y el porcentaje de curaciones elevado.

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# THE URINARY EXCRETION OF AMINO ACIDS. I BY NORMAL MALE SUBJECTS ON CONTROLLED LOW- AND HIGH-PROTEIN DIETS<sup>1,2,3</sup>

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## INTRODUCTION

The purpose of this investigation was to compare the urinary excretion of amino acids of normal males with that of male subjects with moderately advanced tuberculosis. It was believed that such a study might provide new knowledge concerning protein deficiencies in the presence of an infection.

A definite relation has been established between hypoproteinemia and lowered resistance to infection, which is partially explained by Cannon (2) as an impaired capacity of animals to produce antibodies after their protein reserves had been depleted by artificial means. With this in mind, some clinicians (3) have given high protein diets to their tuberculous patients. It was found that the diets apparently increased muscle tone and decreased the period of hospitalization.

In preliminary experiments appreciable differences were found between the two groups, but it was considered desirable to repeat the experiments using rigidly controlled diets. The normal ranges of the urinary amino acids reported previously (4 to 10) have varied rather widely although they have provided a reasonable basis for clinical studies (11 to 13) of liver disease, cystinuria, and other disorders in which there were marked changes from the normal amino acid output.

## EXPERIMENTAL

Data are reported in the present paper from experiments with normal male subjects maintained on fixed high- and low-protein diets of the caloric value. The daily food intake of each subject was adjusted to an amount equivalent to 1.36 Gm of protein per Kg of body weight on the high-protein diet and to 0.70 Gm on the low-protein diet. The high-protein intake was the same as that of tuberculous patients at The Charles Cook Hastings Home. The low-protein intake was selected as that which, it was assumed, would maintain the subjects in nitrogen equilibrium.

Each of the 9 volunteer male subjects was maintained four days on the low-protein diet<sup>4</sup> and approximately 15 ml of water per Kg of body weight per day.

<sup>1</sup> From the Chemical Laboratory, University of California, Los Angeles, California, and The Charles Cook Hastings Home, Altadena, California.

<sup>2</sup> Paper 57. For Paper 56 see Camien and Dunn (1).

<sup>3</sup> This work was aided by a grant to one of us (M S D) from the John and Mary R Markle Foundation.

<sup>4</sup> The same food, cooked in the laboratory, was eaten at the same time by all subjects in quantities proportional to their body weights.

Twenty-four-hour urine samples were collected on the third and fourth days. All samples were preserved under toluene and were refrigerated. All of the subjects were moderately active during the experiments. The same 9 subjects were

TABLE 1  
*Composition of Low-protein Diets*  
(Gm per 70 Kg body weight)\*

1		2	
Bread, white†	75-LD	Banana	100-D
Butter	30-BLD	Bread, white	75 LD
Cake, white with chocolate icing	87-L	Butter	60-BLD
Coffee cake with icing	70-B	Cake, white with chocolate icing	87-L
Corn, canned	100-B	Coffee cake with icing	70-B
Cream	65-BLD	Cream	50 BLD
Hamburger	32-D	Doughnut	50-D
Ice cream, vanilla	71-L	Fish, tuna	46-D
Lettuce	10 D	Ham, deviled	40-L
Mayonnaise	14-D	Ice cream, vanilla	71-L
Orange Juice†	360-B	Lettuce	10-D
Peaches, canned	50-D	Mayonnaise	14-D
Peanut butter	30-L	Noodles, canned	120-D
Pudding, chocolate	100-D	Orange Juice	360 B
Sugar	20 BLD	Sugar	20 BLD
Spaghetti with tomato sauce	220 D	Tomato Juice†	200-L
Tomato juice	200 L		

3			
Bacon	10 L	Jelly	30 D
Bread, white	75-LD	Lamb chop	55 D
Butter	40-BLD	Lettuce	10 D
Cake, white with chocolate icing	87-L	Mayonnaise	11 D
Coffee cake with icing	70 B	Orange juice†	360 B
Cream	50-BLD	Pears, canned	50 D
Doughnut	50-D	Pears, canned	100 D
Eggs, boiled	50 L	Potato, baked	100 D
Ice cream, vanilla	71-L	Sugar	20 BLD
		Tomato juice	200 L

\* Coffee, 135 ml at each meal

B, breakfast L, lunch D, dinner

† 50 Gm at L and 25 Gm at D. Other foods taken at more than one meal divided uniformly

‡ Half taken at 2:30 p.m.

maintained similarly on the high-protein diet. The composition of the low- and high-protein diets is given in tables 1 and 2.

The microbiological procedures and techniques were those described previously.<sup>1</sup> The solutions were compensated for  $\text{NH}_4\text{Cl}$  as well as  $\text{NaCl}$ . Urea was removed by urease.

<sup>1</sup> The microbiological procedures employed are described in a paper by Dunn et al., *Publications in Physiology*, University of California Press, 1959, 8, 203 to 225.

treatment from the unhydrolyzed urines containing amino acids (isoleucine, leucine, lysine, methionine, valine, and threonine) at relatively low concentrations. The mean deviations from the mean values for the different levels of samples averaged about 4 per cent for most of the assays. The microbiological data are given in tables 3 to 5.

## RESULTS

It may be seen (table 3) that the total percentages of twelve amino acids determined in hydrolysates of representative samples of the high- and low-protein diets differed by a factor of approximately 2.4. It is also evident (table 3) that the proportions of the amino acids were different in the two diets. This unintentional variation in the quality of the dietary proteins illustrates the need of

TABLE 2  
*Composition of High-protein Diets*  
(Gm per 70 Kg body weight)\*

Bacon	20 D	Ice cream, vanilla	72-L
Beans, string	75-L	Lettuce	30-LD
Beef, roast	60-L	Milk, homogenized†	960-BLD
Bread, white‡	75 LD	Orange juice‡	360-B
Butter	20-BLD	Peaches, canned	50-L
Carrots	20 D	Pears, canned	50 D
Cake, white with icing	50-D	Potato, baked	70-L
Celery	20 L	Soup, chicken noodle canned	120-D
Corn flakes	15-B	Strawberries, frozen	30-L
Cottage cheese	30-D	Sugar	10-BLD
Crackers	10 §	Toast, whole wheat	25-B
Cream	100-BLD	Tomato	40-D
Eggs, fried	100-B		

\* Coffee, 65 ml each meal

B, breakfast L, lunch D, dinner

† 50 Gm at L and 25 Gm at D. Other foods taken at more than one meal divided uniformly.

‡ Half taken at 2:30 p.m.

§ Taken at 8:00 p.m.

¶ One-fourth taken at 8:00 p.m.

dietitians for accurate information on the amino acid composition of different dietary protein sources<sup>6</sup>.

Both hydrolyzed and unhydrolyzed urine samples were studied in the present investigation because of the possibility that results obtained on unhydrolyzed samples may be of clinical importance (when compared with levels determined on unhydrolyzed samples from pathological cases). It is recognized, however, that amino acid values determined microbiologically in unhydrolyzed urine do not represent values for "free amino acids" or for any other (at present) definable entities. For convenience, values found for unhydrolyzed urines have been reported as "amino acid" values in the present paper. It should be qualified,

<sup>6</sup> The diets were calculated by Emma J. Hollett, dietitian of the Charles Cook Hastings Home.



therefore, that these values (for unhydrolyzed urine) refer only to resultant activities from unknown mixtures of amino acid complexes and free amino acids. Although it is evident that acid hydrolysis greatly reduces the possible number of substances which may have variable amino acid activity, some compounds closely related to the amino acids (perhaps the corresponding hydroxy and keto acids) may be present, even in hydrolyzed urine. It is important, therefore, that analytical methods of the highest possible specificity be selected for the study of such samples. That the microbiological methods probably are more specific than the chemical methods which have been applied to urine has been pointed out by some workers (15).

TABLE 3  
*Dietary Amino Acids\**

AMINO ACID	GM CONSUMED PER DAY		PER CENT OF TOTAL DETERMINED		PER CENT DIFFERENCE†
	Diet IA	Diet II	Diet IA (B)	Diet II (C)	
Arginine	1 56	4 24	4 7	5 3	13
Aspartic Acid	4 62	8 92	14 0	11 0	-21
Glutamic Acid	11 0	20 7	33 0	26 0	-21
Glycine	1 36	4 04	4 1	5 0	22
Histidine	0 90	2 44	2 7	3 0	11
Isoleucine	2 00	5 76	6 1	7 2	18
Leucine	3 10	8 88	9 4	11 0	17
Lysine	1 92	7 36	5 8	9 2	59
Methionine	0 80	2 20	2 4	2 7	12
Phenylalanine	1 84	4 68	5 6	5 8	4
Threonine	1 70	4 80	5 2	6 0	15
Valine	2 16	6 24	6 6	7 8	18
Total	32 96	80 22	100 0	100 0	

\* One tenth the quantity of each food component (except coffee and sugar) consumed daily per 70 Kg. subject was taken, the aliquots were mixed with 300 ml. of 12 N HCl and the mixture was refluxed for 20 hours. The amino acids were determined by microbiological assay.

$$\dagger [(C) - (B)] \times 100/(B)$$

The daily output (hydrolyzed urines) of each amino acid per individual was nearly constant on two successive days for each of the fixed diets (table 5). The values for 12 amino acids and 9 subjects differed from the means by approximately 5 per cent on the low-protein diet and by approximately 6 per cent on the high-protein diet. The comparable values for amino acids in unhydrolyzed urines were each approximately 10 per cent (table 1). That the latter values were somewhat larger than the former was not unexpected because of the probability that the proportions, as well as the microbiological activities, of metabolites in unhydrolyzed urines would be variable.

The excretion (hydrolyzed urines, table 5) of each amino acid by the different individuals deviated from the mean values by 9.0 (3.7 to 17.1) per cent on the

low-protein diet and by 13.5 (6.3 to 19.6) per cent on the high-protein diet. This degree of inconsistency may indicate a normal variation between adult males in the utilization and excretion of amino acids. In general, the excretion (hydrolyzed urine) of amino acids on the rigidly controlled high-protein diet

TABLE 4

*Amino Acids in Unhydrolyzed Urines Excreted on Low- and High-protein Diets\**

(Values given as mg per 24 hours per 70 Kg body weight)

AMINO ACID†	LOW PROTEIN DIET				HIGH PROTEIN DIET				
	Average of M D M per individual‡	Range§	Mean¶ (A¹)	M D M for (A¹)	Average of M D M per individual‡	Range§	Mean¶ (B¹)	M D M for (B¹)	Increase of (B¹) over (A¹)
	per cent			per cent	per cent			per cent	per cent
Arginine	8.8	13 to 20	16	15.7	7.1	17 to 24	20	8.0	25
Cystine	4.0	50 to 88	66	9.5	9.7	174 to 332	236	14.6	258**
Glutamic Acid	7.2	21 to 28	24	8.4	6.5	16 to 23	19	11.8	21**
Glycine	6.8	527 to 966	746	13.0	10.2	525 to 1,169	968	16.7	30
Histidine	15.0	44 to 136	91	26.3	5.4	76 to 212	145	17.8	59
Lysine	19.9	13 to 29	21	21.8	26.9	10 to 43	27	40.0	29
Phenylalanine	7.2	5 to 19	11	22.7	7.2	7 to 14	11	16.2	0
Tryptophan	4.5	8 to 22	14	21.6	8.2	13 to 29	20	17.8	43
Tyrosine	16.0	11 to 26	17	30.5	10.4	13 to 27	22	18.4	29
Average	9.9			18.8	10.2			17.9	31

\* Summary of data obtained from nine normal males. The weight (lbs) and the age (years), respectively, of each subject were 190.26, 185.27, 175.26, 155.26, 155.25, 149.26, 140.29, 135.26, and 135.26. No correlation was noted between the weights or ages of the subjects and their excretions, calculated in mg per 24 hours per 70 Kg body weight.

† Values are omitted for some amino acids which could not be determined with satisfactory accuracy. Maximum values found for these amino acids were 10 (aspartic acid), 22 (isoleucine), 29 (leucine), 18 (methionine), 25 (threonine), and 13 (valine).

‡ The per cent mean deviation from the mean was calculated for each individual's average excretion. The values given are the averages of these calculated percentages.

§ Range of average values for nine subjects.

¶ Mean of average values for nine subjects.

|| Calculated as  $[(B^1) - (A^1)] \times 100 / (A^1)$ .

\*\* Omitted in calculating the average.

employed in the present experiments was not markedly different or more constant than that found by Woodson *et al* (7) for 18 subjects (13 males) on usual dietary regimens.

The excretion (unhydrolyzed urines, table 4) of each amino acid by the different individuals deviated from the mean values for 7 amino acids by 18.8 (8.4 to 30.5) per cent on the low-protein diet and by 17.9 (8.0 to 40.0) per cent on the high-protein diet. That these deviations are greater than those found for the corresponding hydrolyzed samples may be explained by differences between the subjects in their metabolism, yielding unlike proportions or types of bound

amino acids. Such dissimilarities would result in different apparent activities (determined before hydrolysis) even though the amounts of amino acids excreted (determined after hydrolysis) were much more constant.

It may be noted that the excretion (unhydrolyzed urines) of amino acids (excluding cystine and glutamic acid) averaged 30 (0 to 59) per cent greater on the high-protein than on the low-protein diet (table 4). Similarly the excretion (hydrolyzed urines) of amino acids (table 5) was 15 (5.0 to 31) per cent greater on the high-protein than on the low-protein diet. It is of interest, also, that the amino acids excreted either on the low-protein or the high-protein diet were

TABLE 5

*Amino Acids in Hydrolyzed Urines Excreted on Low- and High-protein Diets\**

(Values given as mg. per 24 hours per 70 Kg. body weight)

AMINO ACID	LOW-PROTEIN DIET				HIGH-PROTEIN DIET				
	Average of M.D.M. per individual†	Range§	Mean¶ (A²)	M.D.M. for (A²)	Average of M.D.M. per individual†	Range§	Mean¶ (B²)	M.D.M. for (B²)	Increase of (B²) over (A²)¶
	per cent			per cent	per cent			per cent	per cent
Arginine.....	3.3	17 to 23	20	7.9	4.8	19 to 24	21	6.3	5.0
Aspartic Acid...	5.9	101 to 126	114	5.3	8.2	103 to 166	135	11.0	18.0
Glutamic Acid..	5.8	234 to 369	297	17.4	5.7	251 to 393	320	13.1	7.7
Glycine.....	7.1	501 to 812	648	12.4	7.8	393 to 921	690	16.4	6.5
Histidine.....	6.7	82 to 156	124	7.5	4.1	92 to 203	162	14.1	31.0
Isoleucine.....	3.8	12 to 15	13	3.7	6.7	10 to 20	14	16.5	7.7
Leucine.....	4.7	18 to 20	19	4.1	3.8	17 to 26	21	12.4	11.0
Lysine.....	6.1	37 to 49	42	7.9	5.3	43 to 67	51	13.4	21.0
Methionine.....	4.8	8 to 13	11	12.4	9.4	9 to 15	12	15.4	9.1
Phenylalanine...	3.6	14 to 20	16	11.4	4.0	16 to 24	20	11.2	25.0
Threonine.....	5.0	27 to 51	38	13.6	5.7	35 to 54	45	12.9	18.0
Valine.....	3.7	22 to 25	23	4.3	9.2	21 to 32	27	19.6	17.0
Average.....	5.0			9.0	6.2			13.5	15.0

\* For Footnotes to table 5, see corresponding footnotes to table 4.

less than 5 per cent of the amino acids ingested as protein in the food (table 3).<sup>7</sup> It may be concluded, therefore, that a large part of the amino acids which are available in excess of the need for protein building and other special functions is utilized by the body for other purposes or is converted to inactive substances before being excreted.

It may be seen that glutamic acid excretion as determined in unhydrolyzed urine was 21 per cent lower on the high-protein diet than on the low-protein

<sup>7</sup> About 10 per cent of ingested DL-methionine is excreted in the urine according to Wheeler and György (15). Methionine excretion was less than one per cent of that supplied by the protein of either diet in the present experiments. This difference seems to support the view that the percentage utilization of an amino acid may depend on the ratio of that amino acid to other amino acids in the diet (16).

diet (table 4) Glutamic acid excretion determined in hydrolyzed urine, however, was 77 per cent higher on the high-protein diet than on the low-protein diet (table 5) Similarly, phenylalanine excretion determined in unhydrolyzed urines (table 4) was the same on both diets, but was 25 per cent higher on the high-protein diet as determined in the hydrolyzed urine (table 5) The remaining amino acids (tables 4 and 5) were higher (either hydrolyzed or unhydrolyzed urines) on the high-protein diet than on the low-protein diet However, the percentage difference in excretion on the high- and low-protein diets was greater for each amino acid (except phenylalanine) determined in the unhydrolyzed urines than in the corresponding hydrolyzed samples These observations indicate that the proportions and types of excreted amino-acid complexes (in unhydrolyzed urine) may be influenced by diet to a greater extent than the amino acids (in hydrolyzed urine) The fourfold increase in cystine excretion (table 4) by normal subjects on the high-protein diet suggests that dietary control is essential in clinical studies on the excretion of this amino acid

#### SUMMARY

A total of 15 amino acids (15 in unhydrolyzed and 12 in hydrolyzed samples) have been determined by microbiological methods in 24-hour urines of 9 normal male subjects maintained in separate experiments on rigidly controlled low-protein and high-protein diets The excretion of (apparent) amino acids was more nearly constant in successive 24-hour urines of the same and different individuals in the hydrolyzed than in the unhydrolyzed urines The excretion of amino acids (hydrolyzed urines) was only about 15 per cent greater on the high-protein than on the low-protein diet even though the amino acids determined in the former diet were about 24 times those in the latter The excretion of amino acids (unhydrolyzed urines) averaged about 30 per cent greater on the high-protein than on the low-protein diet except for cystine, which increased about fourfold, and glutamic acid, which decreased about 21 per cent In general, the amounts of amino acids excreted on the rigidly controlled high-protein diet were not markedly different than those found by earlier workers for subjects maintained on arbitrary dietary regimens It appears that the amino acid excretion of adult males normally is inconstant although within limits which have been reasonably well defined in the experiments of the present as well as of earlier investigators

#### SUMARIO

##### *Excreción Urinaria de Ácidos Amínicos en Varones Normales a Dietas Ricas y Pobres en Proteína, Comprobadas*

Un total de 15 amino-ácidos (15 en muestras sin hidrolizar y 12 en las hidrolizadas) fué determinado con técnicas microbiológicas en las orinas de 24 horas de 9 varones normales, mantenidos en experimentos independientes a dietas ricas y pobres en proteína, rigidamente comprobadas La excreción de ácidos amínicos (aparentes) fué más cuasiconstante en las orinas sucesivas de 24 horas de los mismos y de distintos individuos en las muestras hidrolizadas que en las

sin hidrolizar. La excreción amino-ácida (orinas hidrolizadas) fué sólo aproximadamente 15 por ciento mayor con la dieta rica que con la pobre en proteína, aunque los ácidos amínicos determinados con la primera representaron unas 2.4 veces los de la última. La excreción amino-ácida (muestras sin hidrolizar) promedió aproximadamente 30 por ciento más con la dieta rica que con la dieta pobre en proteína, salvo por la cistina, que aumentó casi el cuádruple, y el ácido glutámico, que disminuyó aproximadamente 21 por ciento. En general, las cantidades de ácidos amínicos excretados con la dieta rica en proteína, rígidamente comprobada, no discreparon mayor cosa de las observadas por investigadores anteriores en sujetos mantenidos con regímenes dietéticos arbitrarios. Según parece, la excreción de ácidos aminados de los varones adultos es normalmente inconstante, aunque dentro de ciertos límites bastante bien definidos en estos, así como en anteriores, experimentos.

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## THE URINARY EXCRETION OF AMINO ACIDS: II. BY TUBERCULOUS MALE SUBJECTS ON CONTROLLED LOW- AND HIGH-PROTEIN DIETS<sup>1</sup>

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### INTRODUCTION

The role that protein nutrition plays in the resistance to tuberculosis is not yet established. It has been found that serum globulin increases abruptly with the onset of the disease (1) and the concentration of albumin drops suddenly in far advanced cases of tuberculosis. The albumin concentration seems to be intimately related to the erythrocyte sedimentation rate (2) which usually becomes increasingly higher as the disease progresses. The object of the work reported in this paper was to discover the differences and similarities of amino acid excretion between two groups on the same protein intake: one group composed of tuberculous subjects, the other of normal individuals. The values obtained for the normal subjects have been reported in the preceding paper in this series (11). The amino acid excretions of the tuberculous patients are tabulated in the present report and comparisons drawn with the results obtained from the normal subjects.

### *Experimental*

The subjects used in this study were all male tuberculous patients with moderately advanced disease who were maintained on strict bed rest at The Charles Cook Hastings Home. The length of time spent in this hospital at the time of the diets ranged between one and eleven months, with an average stay of seven months. None of them had been treated by surgical means or streptomycin. These factors kept outside influences at a minimum, so that any results obtained were, as far as possible, the direct result of the diets consumed.

The diets were exactly the same as those discussed and tabulated in the preceding paper (11). In the first half of the experiment, 10 patients were maintained four days on the low-protein diet, consisting of 49 Gm. of protein per 70 Kg. of body weight daily. The vitamin and mineral levels were adequately maintained<sup>2</sup>; total calories were 2,500 and the fluid intake was restricted to approximately one liter per day. Twenty-four-hour urine samples were collected on the fourth day. The same 10 patients were maintained four days on the high-protein diet consisting of 95 Gm. of protein per 70 Kg. of body weight in the second half of the experiment. Calorie and fluid intake were kept the same as in the preceding experiment. Twenty-four-hour urine samples were collected on

<sup>1</sup> From The Charles Cook Hastings Home, Altadena, California, and the Chemical Laboratory, University of California, Los Angeles, California.

<sup>2</sup> Four of the patients were receiving supplements of vitamins A and C.

the fourth day and all samples were preserved under toluene and refrigerated. The figure of 95 Gm of protein used in the high-protein diet was arbitrarily chosen because that is the average amount present in the daily diet of patients in this hospital.

The amino acids were determined by the microbiological procedures described in papers (3, 4, and 10). The samples were treated in the same manner as dis-

TABLE 1  
*Amino Acids in Unhydrolyzed Urines from Tuberculous Patients on Low- and High-protein Diets\**

(Values given as mg per 24 hours per 70 Kg body weight)

AMINO ACID†	LOW PROTEIN DIET			HIGH PROTEIN DIET			
	Range‡	Mean¶ (A <sup>3</sup> )	M D M for (A <sup>3</sup> )	Range‡	Mean¶ (B <sup>3</sup> )	M D M for (B <sup>3</sup> )	Increase of (B <sup>3</sup> ) over (A <sup>3</sup> )
			per cent			per cent	per cent
Arginine	12 to 23	16	20.6	10 to 23	18	21.1	12.5
Cystine‡	202 to 426	288	16.5	203 to 655	437	13.0	51.7**
Glutamic Acid	14 to 32	22	21.2	12 to 30	18	18.2	-18.3**
Glycine	465 to 850	688	18.3	489 to 1,109	868	16.9	26.2
Histidine	92 to 200	137	19.3	105 to 282	190	22.2	38.7
Lysine	27 to 99	50	29.7	31 to 165	70	45.8	40.0
Phenylalanine	10 to 19	15	18.8	12 to 23	16	12.7	6.7
Tryptophan‡	14 to 30	19	18.3	19 to 31	23	11.3	21.1
Tyrosine‡	18 to 51	31	26.1	23 to 59	38	26.4	22.6
Average			21.0			20.8	24.0

\* Summary of data obtained from 10 tuberculous males. The weight (lbs) and age (years), respectively, of each subject were 175-24, 159-27, 176-36, 157-20, 178-25, 208-28, 191-38, 177-21, 169-20, 167-26.

† The following amino acids were also determined on all the unhydrolyzed urine samples with the following maximum values: 71 (aspartic acid), 53 (isoleucine), 30 (leucine), 22 (methionine), 38 (threonine), 30 (valine).

‡ Cystine, tryptophan and tyrosine were assayed only on unhydrolyzed samples because of their partial destruction on acid hydrolysis.

§ Range of average values for 10 tuberculous subjects.

¶ Mean of average values for 10 tuberculous subjects.

|| Calculated as  $[(B^3) - (A^3)] \times 100 / (A^3)$ .

\*\* Omitted in calculating the average.

cussed in the preceding paper. The mean deviations from the mean values for the different levels of samples averaged between 4 and 5 per cent.

## RESULTS

In making a comparison of the tuberculous and normal subjects, the following points were noted. The percentage increase of amino acid excretion resulting from the higher protein intake averaged 24.1 per cent<sup>3</sup> (6.7 to 40.0) on the unhydrolyzed samples of the tuberculous patients (table 1). The percentage in-

<sup>3</sup> Cystine and glutamic acid percentages excluded.



crease for the normal subjects under the same circumstances averaged 30.0% (0.0 to 59.0, table 4, preceding paper (11)). On the hydrolyzed samples, the tuberculous subjects averaged 3.1 per cent (-13.5 to 19.4, table 2), while the normal subjects averaged a 15.0 per cent (5.0 to 31.0, table 5, preceding paper (11)) increase in amino acid output over the low protein diet.

It was found that the glutamic acid excretion of the tuberculous subjects was similar to that of the normal subjects in that, although there was a decrease in the per cent excretion on the high-protein diet (-18.3, unhydrolyzed

TABLE 2  
*Amino Acids in Hydrolyzed Urines from Tuberculous Patients on Low- and High-protein Diets\**

(Values given as mg per 24 hours per 70 Kg body weight)

AMINO ACID	LOW PROTEIN DIET			HIGH PROTEIN DIET			
	Range†	Mean‡ (A <sup>4</sup> )	M D M for (A <sup>4</sup> )	Range†	Mean‡ (B <sup>4</sup> )	M D M for (B <sup>4</sup> )	Increase of (B <sup>4</sup> ) over (A <sup>4</sup> )§
Arginine	20 to 33	26	9.0	24 to 31	26	5.7	0.0
Aspartic Acid	64 to 175	124	15.0	121 to 157	138	6.6	11.3
Glutamic Acid	209 to 514	328	19.2	229 to 401	341	10.2	4.0
Glycine	491 to 780	635	11.2	335 to 703	549	19.0	-13.5
Histidine	120 to 204	160	14.0	122 to 288	191	15.4	19.4
Isoleucine	11 to 20	14	14.0	14 to 17	15	7.2	7.1
Leucine	17 to 32	21	14.6	14 to 23	19	12.0	-9.5
Lysine	42 to 117	62	21.5	41 to 127	69	26.7	11.3
Methionine	8 to 14	11	19.2	8 to 14	11	17.7	0.0
Phenylalanine	11 to 33	22	19.0	20 to 29	23	8.9	4.5
Threonine	34 to 61	46	15.3	36 to 65	49	16.5	6.5
Valine	17 to 32	22	15.0	16 to 25	21	8.4	-4.5
Average			15.6			12.9	3.1

\* See Note 1 for table 1

† Range of average values for 10 tuberculous subjects

‡ Mean of average values for 10 tuberculous subjects

§ Calculated as  $[(B^4) - (A^4)] \times 100 / (A^4)$

samples), this was reversed and the glutamic acid excretion was increased by 4.0 per cent on the high-protein diet when the samples were hydrolyzed. Cystine had the highest percentage increase of any of the amino acids with 51.7 per cent over the low-protein diet excretion. This was much lower, however, than the normal subjects, whose cystine excretion on the high-protein diet was 258 per cent higher. Since the cystine output was so much higher on the low-protein diet of the tuberculous patients (288 mg per 24 hours per 70 Kg) than that of the normal subjects (66 mg per 24 hours per 70 Kg), it would seem to indicate that the tuberculous patients do not retain this sulfur-containing amino acid as well as the normal subjects, or that they have a greater need for

it, possibly because of its combination and subsequent excretion as a detoxifying agent

In table 3 is shown the percentage change between the tuberculous and normal subjects. On the low-protein diet, using the unhydrolyzed samples, cystine was found to be increased fourfold by the tuberculous subjects (336 per cent). When the high-protein diet was used, the percentage increase was not quite

TABLE 3

*Differences in Amino Acid Excretion of Tuberculous and Normal Subjects on Low- and High-protein Diets*

(Values given as mg per 24 hours per 70 Kg body weight)

AMINO ACID	UNHYDROLYZED URINES				INCREASE OF TB OVER NORM SUBJECTS		HYDROLYZED URINES				INCREASE OF TB OVER NORM SUBJECTS	
	Norm Subj		TB Subj		Low* per cent	High† per cent	Norm Subj		TB Subj		Low‡ per cent	High§ per cent
	Low A¹ Mean	High B¹ Mean	Low A² Mean	High B² Mean			Low A² Mean	High B² Mean	Low A⁴ Mean	High B⁴ Mean		
Arginine	16	20	16	18	0.0	-10.0	20	21	26	26	30.0	23.8
Aspartic Acid	—	—	—	—	—	—	114	135	124	138	8.8	2.2
Cystine	66	236	288	437	336.4¶	85.2¶	—	—	—	—	—	—
Glutamic Acid	24	19	22	18	-8.3	-5.3	297	320	328	341	10.4	6.6
Glycine	746	968	688	868	-7.8	-10.3	648	690	635	549	-2.0	-20.4
Histidine	91	145	137	190	50.5	31.0	124	162	160	191	29.0	17.9
Isoleucine	—	—	—	—	—	—	13	14	14	15	7.7	7.1
Leucine	—	—	—	—	—	—	19	21	21	19	10.5	-9.5
Lysine	21	27	50	70	138.1	159.3	42	51	62	69	47.6	35.3
Methionine	—	—	—	—	—	—	11	12	11	11	0.0	-8.3
Phenylalanine	11	11	15	16	36.4	45.5	16	20	22	23	37.5	15.0
Threonine	—	—	—	—	—	—	38	45	46	49	21.1	8.9
Tryptophan	14	20	19	23	35.7	15.0	—	—	—	—	—	—
Tyrosine	17	22	31	38	82.4	72.7	—	—	—	—	—	—
Valine	—	—	—	—	—	—	23	27	22	21	-4.3	-22.2
Average					40.9	37.2					16.4	4.7

\* Calculated as  $[(A^2) - (A^1)] \times 100 / (A^1)$

† Calculated as  $[(B^2) - (B^1)] \times 100 / (B^1)$

‡ Calculated as  $[(A^4) - (A^2)] \times 100 / (A^2)$

§ Calculated as  $[(B^4) - (B^2)] \times 100 / (B^2)$

¶ Omitted in calculating the average

twofold (85.2 per cent). The values for lysine showed the next highest percentage increase of tuberculous over normal subjects with 138 per cent on the low-protein diet and 159 per cent on the high-protein diet. This was reduced to 47.6 and 35.3 per cent, respectively, however, when the hydrolyzed samples were examined.

Although the values for cystine deviated the most strikingly from the normal, it is noteworthy that, on the whole, the excretion of most of the amino acids was increased on both diets by the tuberculous subjects when the unhydrolyzed sam-

ples were assayed with an average increase of 40.9 on the low-protein and 37.2 per cent on the high-protein diet. Glutamic acid and glycine were the only exceptions<sup>4</sup> with slight decreases for both of them. The amounts of glutamic acid found in the hydrolyzed samples reversed this trend, but glycine was still slightly decreased in amount.

The average percentage increase of the amino acids excreted by the tuberculous patients over the nontuberculous subjects was lowered when the hydrolyzed samples were assayed. On the low-protein diet, the average percentage increase was 16.4 while on the higher amount it was only 4.7 per cent. The fact that the average amino acid excretion of the tuberculous over the normal subjects was persistent, although small, would seem to indicate some difference in metabolism between the two groups. The larger difference when the unhydrolyzed samples were used might be explained, as in the preceding paper (11), where the possibility that there was a difference in the amount of bound amino acids was set forth. This difference was lowered when the hydrolyzed samples were used and the average 4.7 per cent increase of the tuberculous over the normal subjects on the high-protein diet is insignificant. It is also noteworthy that, when the amounts of the amino acids excreted by the normal and tuberculous subjects were compared, the tuberculous subjects excreted proportionately larger amounts of amino acids on the low-protein diet than they did on the high-protein diet.

In drawing a parallel between the two groups of subjects, it might be said that there were relatively greater differences in amino acid excretion on a group basis than on the amount of protein ingested. Woodson *et al.* (5) also reported no significant variations in amino acid excretion, although their subjects were on a wide variety of "normal" diets. The same observation was made by Yeh *et al.* (6), who assayed the amino acid excretion of 7 normal females, and found a remarkably uniform pattern in spite of dietary and age differences.

Cystinuria was the most marked deviation found in the tuberculous subjects. The cystine levels attained by these patients were as high as those found by several workers investigating the cystine excretion of cystinurics. Bodansky and Bodansky (7) reported levels between 400 and 1,000 mg. for cystinuric subjects while Yeh *et al.* found an average excretion of 291 mg. per twenty-four hours on one patient who was tested on seven consecutive days. In trying to find a correlation between cystine excretion and the relative toxicity of the individual tuberculous infections no conclusions could be drawn.

Since cystine is one of the end products of the metabolism of methionine, the problem may be one involving this amino acid rather than of cystine alone. Brand and co-workers (8 and 9) found that the cystinuric individual was capable of using almost completely large amounts of cystine fed as the free amino acid. On the contrary, methionine or cystine, when fed, increased the output of cystine. In an attempt to establish whether the large amount of cystine present in the urine of tuberculous patients was due to detoxification with cystine or due to incomplete metabolism of amino acid sulfur, it was decided to assay the

<sup>4</sup> Glycine values decreased 8.3 per cent on low protein and 5.3 per cent on high protein, glutamic acid values decreased 7.8 per cent on low-protein and 10.3 on high protein diet.

twenty-four-hour samples from tuberculous subjects for inorganic sulfates, etheral sulfates, and neutral sulfur before and after giving them extra methionine. The results from this work will be reported at a later date.

#### SUMMARY

1 Microbiological assays were performed on 24-hour urine specimens from 10 male subjects with moderately advanced tuberculosis for fifteen amino acids (15 on unhydrolyzed and 12 on hydrolyzed samples).

2 The results were compared with those obtained on 9 normal male subjects reported in the preceding paper (11), and the following points were noted:

(a) The normal patients had an average increase of 30.0 per cent in amino acid excretion due to the high protein diet as compared to a 24.1 per cent increase by the tuberculous subjects (unhydrolyzed samples).

(b) On the hydrolyzed samples, the normal subjects increased their amino acid excretion as a result of the high protein diet by 15.0 per cent as compared to 3.1 per cent by the tuberculous.

(c) The highest percentage increase (51.7) of any of the amino acids resulting from diet alone was observed for cystine.

(d) The average cystine output of the tuberculous subjects on the low-protein diet was 288 mg per 24 hours per 70 Kg of body weight, as compared to 66 mg by the normal subjects. On the high-protein diet, the tuberculous subjects excreted 437 mg as compared to 236 by the normals. This was found to be a fourfold increase over the normal subjects on the low-protein diet (336 per cent) and almost twofold increase on the high protein diet (85.2 per cent).

(e) Some difference in the metabolism of the other amino acids between the two groups was suggested by the small but persistent average increase in amino acid excretion by the tuberculous subjects.

#### SUMARIO

##### *Excreción Urinaria de Ácidos Aminoácidos por Varones Tuberculosos con Dietas Ricas y Pobres en Proteína*

1 En ejemplares de orina de 24 horas, procedentes de 10 sujetos varones con tuberculosis moderadamente avanzada, ejecutáronse valoraciones microbiológicas en busca de 15 amino-ácidos (15 en muestras sin hidrolizar y 12 en las hidrolizadas).

2 Al comparar el resultado con el obtenido en 9 varones normales, y descrito en el trabajo anterior, notáronse los siguientes puntos:

(a) Los sujetos normales mostraron un aumento medio de 30.0 por ciento en la excreción de amino-ácidos, debido a la dieta rica en proteína, comparado con 24.1 por ciento en los tuberculosos (muestras sin hidrolizar).

(b) En las muestras hidrolizadas, los sujetos normales aumentaron, por virtud de la dieta rica en proteína, su excreción de ácidos aminoácidos en 15.0 por ciento, comparado con 3.1 por ciento en los tuberculosos.

(c) De todos los amino-ácidos, la cistina fué el que mostró mayor aumento porcentario (51.7), por virtud de la dieta solamente.

(d) La excreción media de cistina por los tuberculosos con el régimen pobre en proteína fué de 288 mg en 24 horas por 70 kg de peso del individuo, comparado con 66 mg en los sujetos normales. Con el régimen rico en proteína, los tuberculosos excretaron 437 mg, comparado con 236 en los normales. El aumento en los tuberculosos, comparados con los sujetos normales, fué, pues, cuádruple con el régimen bajo en proteína (336 por ciento) y casi doble (85.2 por ciento) con el rico en proteína.

(e) El pequeño, pero persistente, aumento medio en la excreción amino-ácida por los tuberculosos indica alguna diferencia en el metabolismo de los otros ácidos amínicos por los dos grupos.

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# STUDIES OF FOOD INTAKE AND REQUIREMENTS OF WOMEN WITH ACTIVE AND ARRESTED TUBERCULOSIS<sup>1 2</sup>

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## INTRODUCTION

As a part of a long time study of the role of nutrition in adult vitality and early senescence, the food patterns of active women from 18 to 80 years of age have been sampled by workers in this laboratory. The dietary practices of these women have been described previously (1). For successive age groups, the mean caloric intakes were as follows: 17 to 25 years, 2,177 calories, 20 to 29 years, 2,180 calories, 25 to 35 years, 1,953 calories, and 40 to 69 years, 1,658 calories. Thus women in the North Central region are accustomed to food patterns with a quantity of food supplying 1,700 to 2,200 calories per day. Thus caloric intake was necessary to provide 60 Gm of protein daily on self-selected diets. Among women over forty years of age, there was some evidence that chronic ill health accompanied dietary inadequacies, particularly calories and protein.

The question of suitable dietary recommendations for women with active and arrested tuberculosis was presented to this laboratory in a request for recommendations for food subsidies for patients discharged from sanatoriums. Although there has been recognition of the difficult feeding problem associated with the tuberculous patient (2), there is little information in the literature concerning the intake and utilization of food by individuals with tuberculosis. Recommendations of 3,000 calories or more per day (3) exceed the amounts of food which moderately active, healthy women eat. Since the diet must be planned in terms of quantities of food which the patient can and will consume, the food intake patterns of women with active and arrested tuberculosis have been studied. The techniques of dietary survey were comparable to those used in similar studies with healthy women so that comparison may be made among the three groups. Information also was obtained concerning the utilization of nitrogen and ascorbic acid by some of the subjects of this study.

## PLAN OF INVESTIGATION

A survey of food habits was conducted at the Ingham County sanatorium in Michigan, with women from ages of 18 to 45. There were two groups of subjects, one included 30 nonambulatory patients with minimal or moderately advanced active tuberculosis, the second group was made up of 35 women with arrested tuberculosis who were former patients of the sanatorium and who attended the outpatient clinic at regular intervals. Eleven of the women with arrested tuber-

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culosis had been readmission cases at the sanatorium and the interval since the last discharge varied from one month to nine years

Through personal interviews, information was obtained about the economic status and food habits and a series of seven daily food records was collected from each subject. The nutritive value of the diets was calculated by the procedure of Donelson and Leichsenring (4) and these values were compared with data for apparently healthy women as reported by Greenwood (5)

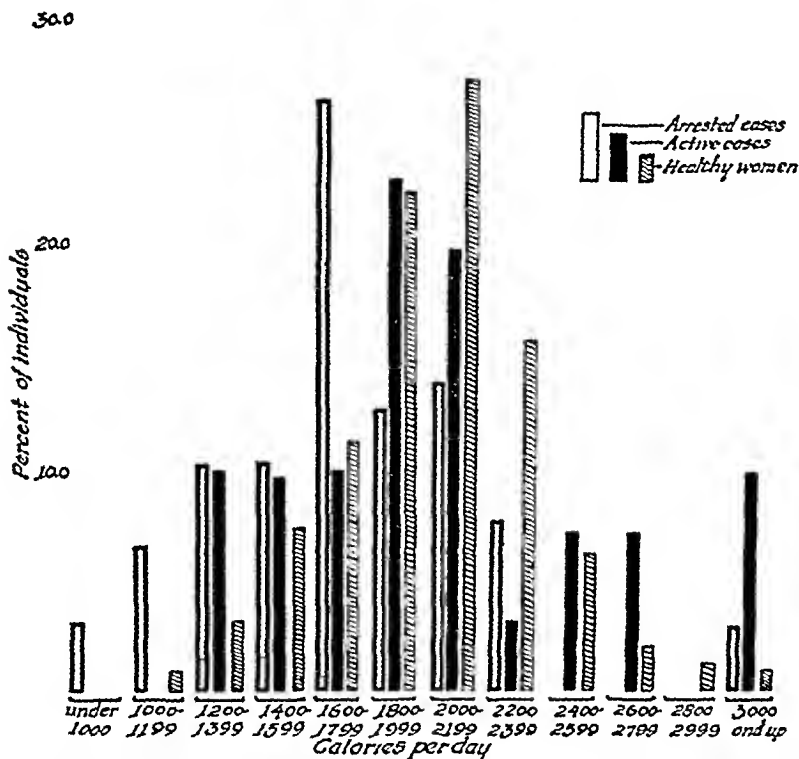


FIG. 1. Distribution of calories in the diets of women with active and arrested tuberculosis, and of healthy women

## RESULTS

The caloric intakes for the three groups are given in figure 1. The daily caloric intakes for healthy women exceeded those for tuberculous women. For the healthy women, the peak of distribution occurred at an intake of 2,000 to 2,199 calories, whereas for women with active tuberculosis the peak of distribution was at an intake of 1,800 to 1,999 calories, and at an intake of 1,600 to 1,799 calories for women with arrested tuberculosis. Sixty per cent of the patients with arrested tuberculosis had daily caloric intakes of less than 1,800 calories, for twenty per cent of the group, the intakes averaged less than 1,400 calories per day.

The intake of food by women with arrested tuberculosis did not vary quantitatively with the degree of physical activity. The factors which did appear to be responsible for the limited food intake were fatigue, lack of adequate finances for household help as well as for food, and lack of appetite. For the patients with active tuberculosis, the factors which were apparently important in limiting food intake were lack of appetite and the desire to control weight.

The protein content of the diets is given in table 1. The proportion of tuberculous women with intakes of protein above 75 Gm. was higher than for healthy women. However, 33 per cent of women with arrested tuberculosis and 38 per cent of women with active tuberculosis had protein intakes less than 62.5 Gm. There was a positive relationship between the protein and caloric contents of the diet. For women with arrested tuberculosis, the correlation coefficient was 0.802 and this was statistically significant.

TABLE 1  
*The Protein Intake of Healthy College Women and Women with Active and Arrested Tuberculosis*

PROTEIN INTAKE PER DAY	HEALTHY COLLEGE WOMEN	WOMEN WITH TUBERCULOSIS	
		Active	Arrested
	per cent	per cent	per cent
Below 50.0 Gm.	8	10	8
50.0 to 62.4 Gm.	31	28	25
62.5 to 74.9 Gm.	46	24	31
75.0 to 87.4 Gm.	14	17	28
87.5 Gm. and above	1	21	8

A comparison of the distribution and occurrence of certain classes of foods in the diets of tuberculous and healthy women is shown in table 2. The patterns of food consumption for the three groups were similar. Twenty-two per cent of the women with arrested tuberculosis had less than one cup of milk daily, whereas 13 per cent had an intake of three or more cups per day. Thirty per cent of the arrested cases averaged less than one serving of meat daily and there was less than one serving of citrus fruit daily in the diets of 52 per cent of the women with arrested tuberculosis.

Since the patterns of food selection by tuberculous women were similar to those for healthy women, it appeared probable that a restricted intake of essential nutrients would parallel the limited caloric intakes. Evidence for this in respect to the diets of women with arrested tuberculosis is shown in table 3. The intakes of various nutrients were less than the amounts recommended by the Food and Nutrition Board of the National Research Council (6) for 76 per cent of the women in the case of iron and thiamine, 64 per cent in the case of vitamin A, and 45 per cent in respect to ascorbic acid. The calcium and riboflavin intakes were closely related to the protein intake, milk was the important source of these nutrients in the diets. Limited usage of cereals and meat restricted the intakes of thiamine and iron.



The analyses of dietaries of women with active tuberculosis represented the selection of food from the diet tray by the individual and were not an evaluation of the adequacy of the hospital diet as it was served. The upper range of values given in the preceding tables probably indicates the quantity of nutrients offered in the sanatorium diet. The differences in intakes for patients eating from the same hospital diet demonstrate an important problem in feeding in tuberculosis, *i e.*, that the patient must be encouraged and educated to eat quantitatively the

TABLE 2

*Percentage Distribution of Tuberculous and Healthy Women According to Occurrence of Certain Foods in Diet*

FOOD GROUP	NUMBER OF TIMES EATEN PER WEEK					
	0	1 to 3	4 to 6	7 to 13	14 to 20	21 or more
	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
Milk						
Women, arrested tuberculosis	3	3	16	32	32	13
Women, active tuberculosis			10	14	52	24
Women, healthy	3	10	16	39	29	3
Green and Yellow Vegetables						
Women, arrested tuberculosis			26	68	3	3
Women, active tuberculosis		3	24	66	7	
Women, healthy	1	9	31	54	5	
Citrus Fruits						
Women, arrested tuberculosis	6	23	23	48		
Women, active tuberculosis		14	17	59	10	
Women, healthy	2	18	37	41	2	
Meat						
Women, arrested tuberculosis			30	61	6	3
Women, active tuberculosis		3	3	62	32	
Women, healthy		2	12	82	5	

food that is provided for him. If good dietary habits are developed during the sanatorium stay, these habits may continue after the disease is arrested.

The food intake patterns for tuberculous women which have been presented reflect the dietary habits of the group. Metabolic data also are necessary, however, for evaluation of the quantitative nutritional requirements. Data were obtained concerning the utilization of nitrogen and of ascorbic acid by women from the group studied in the survey.

*Nitrogen retentions of tuberculous women.* Six women with moderately advanced, active, afebrile tuberculosis whose sputum contained tubercle bacilli were subjects for nitrogen balance studies for a period of fifteen weeks. There were five,

seven-day balance periods, each preceded by a period of fourteen days for dietary adjustment. The protein content of the usual hospital diet was varied by adjustment of the milk intake of the different periods. Weighed food consumption

TABLE 3  
*The Calcium, Iron, Protein, and Vitamin Content\* of Diets of 53 Women  
with Arrested Tuberculosis*

NUTRIENT	NUMBER INDIVIDUALS
Calcium	
0.8 Gm. and above	10
0.5 to 0.79 Gm.	8
Less than 0.5 Gm.	6
Riboflavin	
1.5 mg. and above	21
1.0 to 1.49 mg.	7
Less than 1.0 mg.	5
Protein	
60 Gm. and above	23
50 to 59 Gm.	7
Less than 50 Gm.	3
Iron	
12 mg. and above	7
9 to 11.9 mg.	17
Less than 9 mg.	9
Thiamine	
1.1 mg. and above	8
0.8 to 1.09 mg.	15
Less than 0.8 mg.	10
Ascorbic Acid	
70 mg. and above	18
45 to 69 mg.	8
Less than 45 mg.	7
Vitamin A	
5,000 I U. and above	12
3,500 to 4,999 I U.	8
Less than 3,500 I U.	13

\* Determined by calculation

records were obtained for both the adjustment and balance periods. During the balance period, weighed samples of food representing an aliquot portion of the amount eaten and all fecal and urinary excretions were collected. These were prepared for analysis according to the procedure of Stearns (7), and nitrogen was determined by the Kjeldahl method (8). The nitrogen content of beverages and

medicine were analyzed and these values included in the total nitrogen intakes. Preliminary analyses of the nitrogen content of sputum indicated that there was no appreciable excretion by this path, therefore collections of sputum were not made.

The mean nitrogen retentions at various protein intakes are given in table 4. Thirty balances are reported. Data for healthy college women are also included. There were wide individual variations among the data for the tuberculous cases.

TABLE 4

*The Nitrogen Retentions of Healthy Women and Women with Active and Arrested Tuberculosis, Averages for Seven-day Balance Periods*

GROUP	NUMBER OF BALANCES	NITROGEN INTAKE		MEAN PROTEIN* INTAKE	MEAN NITROGEN RETENTION	NUMBER IN NEGATIVE BALANCE
		Range	Mean			
		Gm /24 hrs	Gm /24 hrs	Gm /24 hrs	Gm /24 hrs	
I Women with active tuberculosis	2	6 00 to 7 99	7 06 $\pm$ 0 51†	44 12	-0 02 $\pm$ 1 14†	1
	13	8 00 to 9 99	9 18 $\pm$ 0 36	57 38	0 73 $\pm$ 0 61	3
	3	10 00 to 11 99	10 61 $\pm$ 0 47	66 31	1 64 $\pm$ 0 24	0
	8	12 00 to 13 99	12 80 $\pm$ 0 31	80 00	1 47 $\pm$ 0 72	0
	4	14 00 to 15 99	14 78 $\pm$ 0 38	92 38	2 16 $\pm$ 0 52	0
II Women with arrested tuberculosis	3	7 00 to 9 99	8 72 $\pm$ 0 72	54 5	0 72 $\pm$ 0 60	1
III Healthy Women	14	6 00 to 7 99	7 11 $\pm$ 0 46	44 44	-0 11 $\pm$ 0 72	7
	10	8 00 to 9 99	8 93 $\pm$ 0 48	55 81	0 28 $\pm$ 0 77	4
	4	10 00 to 11 99	10 97 $\pm$ 0 88	68 56	1 06 $\pm$ 0 55	0
	2	12 00 to 13 99	13 74 $\pm$ 0 23	85 88	2 13 $\pm$ 0 20	0
	1	14 00 to 15 99	15 68 $\pm$ 0 00	98 00	1 56 $\pm$ 0 00	0
(b) McKay‡ (12)	17	6 00 to 7 99	7 37	46 06	-0 64	14
	45	8 00 to 9 99	9 09	56 81	0 23	15
	41	10 00 to 11 99	10 82	67 62	1 08	5
	14	12 00 to 13 99	12 60	78 75	1 40	0
	6	14 00 to 17 58	15 46	96 62	2 74	0

\* Protein = Nitrogen  $\times$  6.25

† Mean deviation

‡ Class intervals combined by calculation

as shown by the mean deviations, however, the mean retentions at different intakes closely paralleled the mean retentions for healthy women. There were four individuals in the tuberculous series with negative nitrogen balance at intakes of 62.5 Gm. or less per day. The others in this series were either at equilibrium, or storing nitrogen above this intake. The retention of nitrogen was increased with intake.

From these data, it would appear that the intake of protein necessary for equilibrium is little or no higher for the tuberculous women than for the healthy

individual For the tuberculous individual, however, an intake of protein adequate for positive nitrogen balance is desirable An intake of 80 Gm of protein would appear to be adequate to permit tissue repair for women with a degree of tuberculous infection similar to these patients A recommended intake of 80 Gm is practical in terms of cost, diet planning, and appetite limitations

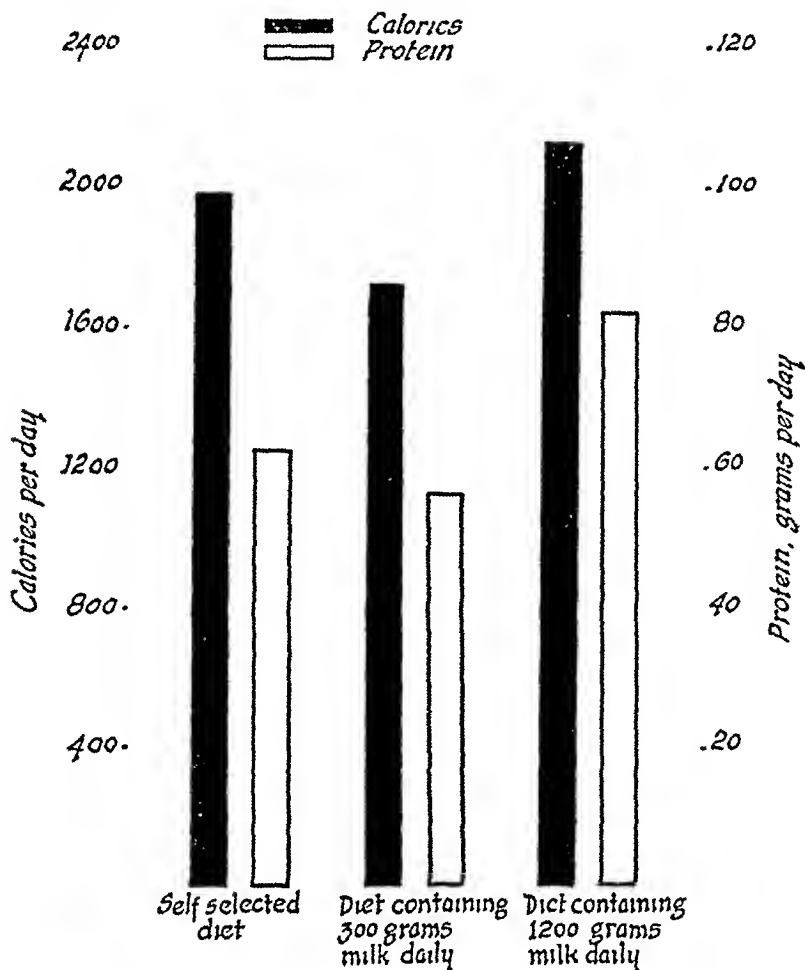


FIG 2 The caloric and protein content of diets of tuberculous women with variation in milk intake

When the milk intake was quantitatively increased from 300 Gm of milk daily to 1,200 Gm for the subjects on the nitrogen balance study, the average caloric intake was increased by 400 calories per day This is shown in figure 2 Although to some extent the patient limited intakes of other foods because of additional milk in the diet, the effect of the increased milk was increased calories and increased intakes of protein and calcium The average weights of the patients were constant on the restricted milk intake and there was an average gain of 2.6 pounds after six weeks on a daily intake of 1,200 Gm of milk

*The urinary excretion of ascorbic acid by tuberculous and healthy women* Lowered values for ascorbic acid in the plasma and the urine have been reported for tuberculous patients as compared with healthy individuals (9, 10) Little attention has been directed, however, toward the ascorbic acid nutrition of patients with

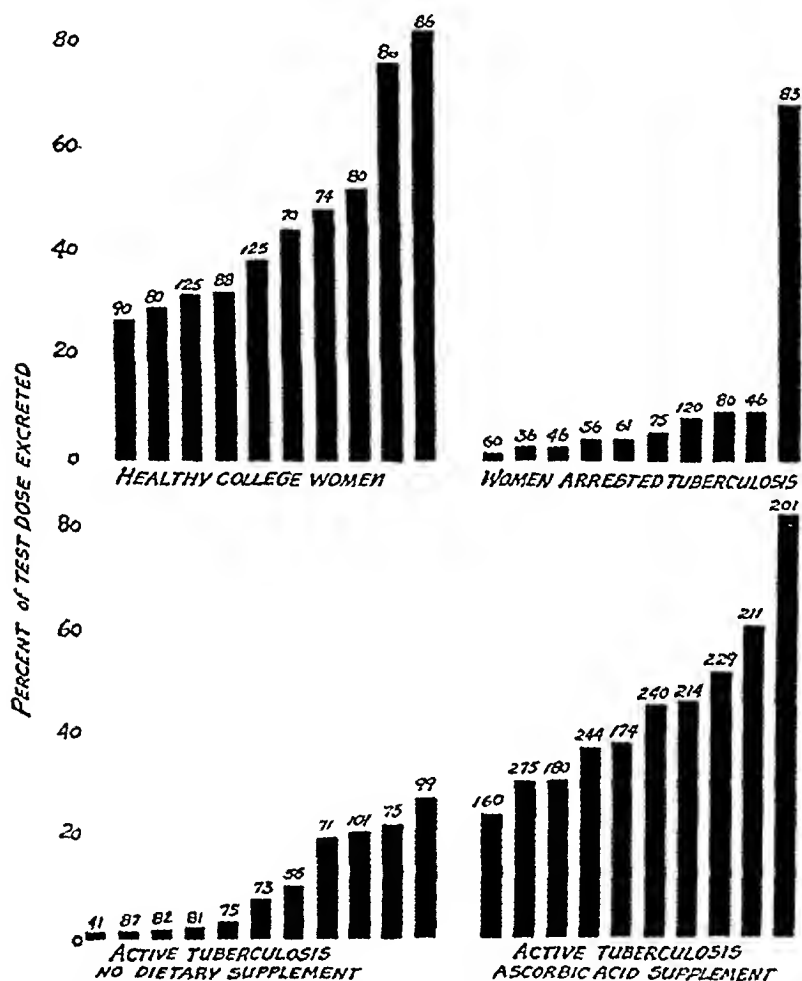


FIG 3 The per cent excretions of a test dose of ascorbic acid by tuberculous and healthy women

arrested tuberculosis In this study the urinary excretion of ascorbic acid following a test dose of 400 mg was used as a technique for studying the utilization of ascorbic acid by tuberculous women Twenty-four-hour urine collections were made on three successive days Reduced ascorbic acid was determined daily by the 2,6 dichlorophenohndophenol method, using a Coleman spectrophotometer On the fourth day a test dose of 400 mg of ascorbic acid was given orally and the ascorbic acid of the following 24-hour urine collection was measured The per cent of the test dose excreted was calculated from the difference between the

excretion before and after the test dose. Data were obtained for women with arrested tuberculosis and bed patients with active tuberculosis. One group of patients with active tuberculosis had received ascorbic acid as a dietary supplement in amounts of 100 mg or more each day for several months preceding the collections. Another group of patients with active tuberculosis had not had ascorbic acid other than that provided by the daily diet. In addition, data were obtained for senior and graduate women who were free from apparent signs of disease and whose chest roentgenograms revealed no evidence of tuberculosis. The results are shown by the bar diagram in figure 3. The intake of ascorbic acid was calculated and the value for each individual is given above the corresponding bar.

The intake of ascorbic acid for the healthy women was from 70 to 125 mg and was supplied entirely by the diet. From 26 to 81 per cent of the test dose was excreted in the urine by this group. The per cent excretions of ascorbic acid by women with active tuberculosis were low where the diet was not supplemented. For the group which had received ascorbic acid supplements, however, the excretions were similar to the excretions of healthy college women on a self-selected, unsupplemented diet.

The intake of ascorbic acid for women with arrested tuberculosis varied from 36 to 120 mg per day. Six of the women had intakes below the amount recommended by the Food and Nutrition Board of the National Research Council (9). The intakes of the others were similar to those for healthy women. The per cent excretions of the test dose for women with arrested tuberculosis were low. Only one individual had a per cent excretion within range of the healthy women. She was a laboratory technician at the hospital, was active socially, and had apparently made a good recovery from the disease.

The low values for the other arrested cases indicate that these women were receiving an inadequate amount of ascorbic acid. The pattern of excretion did not differ greatly from the pattern for women with active tuberculosis on an unsupplemented diet. The number of total values is small for a survey measurement such as the per cent excretion of a test dose. The results indicate, however, that the disturbed metabolism of ascorbic acid in tuberculosis may continue after arrest of the disease and that the ascorbic acid requirement may exceed that of healthy women.

The findings reported here indicate that the recommendations for feeding women patients with tuberculosis need to be directed toward consideration of the disease as one which requires a long time for the healing process to be accomplished. As a consequence, it is necessary for the patient to develop food habits which will allow quantitative intake of nutrients for the rest of her life. With the exception of ascorbic acid, the evidence of increased food requirements in tuberculosis is not as striking as the evidence for the necessity to encourage the tuberculous patient to eat the kind and amounts of food required by normal women. Dietary recommendations providing for an intake of 2,000 to 2,200 calories with 80 Gm of protein daily appear to be sound from the standpoint of recovery from tuberculosis and also from the standpoint of food habits which the subject may

be expected to continue for a prolonged period. The lowered total intake of food by women with arrested tuberculosis also indicates that a unit of nutrition education should be a part of the rehabilitation program for this group.

#### SUMMARY

A survey was made of the food habits of 30 women with active tuberculosis and 35 women with arrested tuberculosis and comparisons have been made with food intakes of healthy women. The caloric intakes for women with active tuberculosis varied from 1,300 to 3,000 calories per day. The average caloric intake for the women with arrested disease was about 300 calories per day less than for healthy women or women with active tuberculosis, although the patterns of food selection were similar. The lowered intake of calories by women with arrested tuberculosis was paralleled by a restricted intake of other nutrients.

Nitrogen retentions were studied for 6 women with active, afebrile tuberculosis. There were five seven-day balance periods for each subject and the protein content of the diets was varied by adjustment of the milk intake. Mean daily nitrogen balances are reported.

The daily urinary excretions of ascorbic acid preceding and following a test dose of 400 mg. ascorbic acid were determined for 10 healthy women, 10 women with arrested tuberculosis, and 10 women with active tuberculosis. The ascorbic acid content of the urine was low for both active and arrested cases on their customary diets and after the test dose. However, ascorbic acid excretions for patients with active tuberculosis who had received dietary supplements of 100 to 300 mg. of ascorbic acid per day for at least two months were similar to those for healthy women.

#### SUMARIO

##### *Estudios de la Ingestión y Requisitos Alimenticios de las Mujeres con Tuberculosis Activa y Estacionada*

Tras una encuesta de los hábitos alimenticios de 30 mujeres con tuberculosis activa y 35 mujeres con tuberculosis estacionada, lucieronse comparaciones con la ingestión alimenticia de mujeres sanas. En lo tocante a calorías, la ingestión de las mujeres con tuberculosis activa varió de 1,300 a 3,000 al día. Para las que tenían la enfermedad estacionada, la ingestión media fué de unas 300 calorías menos, aunque la selección de alimentos se conformó a un patrón semejante. La ingestión menor de calorías por las mujeres con tuberculosis estacionada se reflejó igualmente en la limitada ingestión de otros elementos nutrientes.

Estudióse la retención de nitrógeno en 6 mujeres con tuberculosis afebril, activa, con cinco períodos equilibrados de siete días para cada sujeto, variándose el contenido de proteína en la dieta por medio del ajuste de la ingestión de leche. Preséntanse las cifras diarias medias de nitrógeno.

La excreción urinaria diaria de ácido ascórbico antes y después de una dosis de ensayo de 400 mg. de dicho ácido fué determinada en 10 mujeres sanas, 10 con tuberculosis estacionada y 10 con tuberculosis activa. El contenido urinario

de ácido ascórbico fué bajo en los casos tanto activos cuanto estacionados con la dieta de costumbre y despues de la dosis de ensayo Sin embargo, la excreción del ácido en las enfermeras con tuberculosis activa que habían recibido complementos dietéticos de 100 a 300 mg diarios de ácido ascórbico por lo menos durante dos meses fué semejante a la observada en mujeres sanas

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# AN APPRAISAL OF THE CONTRIBUTION OF MASS RADIOGRAPHY IN THE DISCOVERY OF PULMONARY TUBERCULOSIS<sup>1</sup>

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## INTRODUCTION

It is proposed in this paper to evaluate the usefulness and the limitations of mass roentgenographic surveys of apparently healthy groups of the population as an instrument of attack upon the prevalence of tuberculosis in a community, such as the city of Baltimore. Through an analysis of a part of the Baltimore City experience with mass chest radiography, the objective of this study is to ascertain to what extent the procedure has demonstrated pulmonary tuberculosis and revealed significant epidemiological differences in the prevalence of tuberculosis in the various groups, to determine what mass radiography has contributed to the discovery of *new* cases of the disease and prompt provision for their medical care and isolation, and to consider its contribution to discovery of cases in the *minimal* stage of the disease in relation to all other means of case notification and discovery available to the health department. This study does not contemplate an assessment of the educational value of such surveys, nor is it concerned with the cost of this method of case finding in comparison with others.

It has long been recognized that the keynote to effective reduction in the prevalence of tuberculosis in any community is early discovery, isolation, and treatment of individuals suffering from active or potentially active pulmonary disease. Under the conditions of medical practice and public health administration which have obtained up to recent years even in the most advanced communities of the United States, progress has been slow in the attainment of this objective. In New York State, for example, Mikol and Plunkett (1) found that, in spite of all efforts to promote earlier diagnosis, the proportion of cases reported in the minimal stage remained at about 20 per cent from 1921 to 1940, and the majority of cases were in the moderately to far advanced stage or dead at the time they came to official attention. With the development of practical and comparatively inexpensive techniques of miniature photography of the chest image on the fluorescent screen (2), a method became available which gave promise of greatly improving this situation. It became possible to examine cheaply, rapidly, and easily large groups of supposedly healthy persons and to discover among them those who were suffering from disease in its minimal stage.

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<sup>2</sup> This report is based on a thesis submitted to the School of Hygiene and Public Health of The Johns Hopkins University in conformity with the requirements for the degree of Doctor of Public Health.

During the past decade, the potentialities of "mass radiography" of the chest of supposedly healthy persons have been explored extensively in this country and abroad and many claims have been put forward regarding the value of this procedure. It has been stated that it not only increases the proportion of cases of tuberculosis which are discovered in the minimal stage of the disease (3), but that it affords an index of measurement of the prevalence of tuberculosis in the community as a whole (4) and points out those groups of the population which are epidemiologically important (5). In addition, by means of periodic re-examinations, it affords an index of incidence (6).

Without attempting to review these reports in detail, it suffices to point out that it is difficult to compare one with another and to judge to what extent these claims have been established. There are many confusing variables. They relate to the manner in which the groups are selected for mass radiography and the extent of participation of the group members (7), the extent to which reading of small films are supplemented by large films (8), the skill and consistency of the film reader (9), the extent to which interpretation of the roentgenogram is supplemented by follow-up clinical and laboratory investigations (10), and, finally, to the criteria used in defining and classifying "cases" of tuberculosis upon which rates and estimates are based (11, 12). While mass radiography of the chest undoubtedly has its place in the epidemiologic attack upon tuberculosis, the values and limitations of this procedure have not yet been clearly delineated.

Baltimore has faced a grave tuberculosis problem for many years. In spite of the fact that mortality from tuberculosis has declined steadily in this city during the past few decades, the death rate in 1946, the year of this study, was 80.3 per 100,000 persons, whereas the national tuberculosis mortality rate for the same year was less than 40. Among white persons in Baltimore, the death rate was 46.7 per 100,000, among Negro residents, who constituted one-fifth of the population and contributed 53 per cent towards the city's mortality from tuberculosis, the death rate was 218.7 per 100,000.

In an effort to expand its tuberculosis control activities, the Baltimore City Health Department began several years ago to explore the use of mass radiography of apparently healthy persons. In the summer of 1944, with the assistance of the United States Public Health Service and the Maryland Tuberculosis Association, the Bureau of Tuberculosis obtained the use of a mobile photo-fluorographic unit equipped to take 35 mm. films (changed in May 1946 for a 70 mm. unit). This unit has been in *continuous* operation since then and has been transported around the city taking chest roentgenograms of various groups of the population. By the end of 1947, approximately 155,000 supposedly healthy persons had been examined in 140 groups of the city's population.

#### METHOD OF INVESTIGATION

The material which has been selected for the purposes of this investigation is derived from the activities of the portable photoroentgen unit in Baltimore during the year 1946. At the time this study was undertaken, sufficient time

had elapsed to make possible final evaluation of the status of the cases found. Accordingly, the data for this year could be analyzed not only as to the results of survey film readings but followed through to determine those individuals who had active tuberculous disease requiring administrative attention.

During the calendar year 1946, fifty groups of apparently healthy people were examined roentgenographically in the mass survey program. A total of 48,175 persons were examined, roughly 5 per cent of the estimated total population of Baltimore City (930,000). The groups were selected by invitation and solicitation or on the basis of requests by the groups themselves. Since the service was not compulsory, only those persons who were interested in having a chest film, or could be persuaded to have one, were examined. There was no selection with respect to ability to pay as the service was free. The groups examined were industrial, office and department store employees, residents of housing projects and various communities, and students in the high schools and colleges. Approximately 80 per cent of the persons who were offered this service at their place of employment participated. The potential populations of the loosely defined "communities" were not known and the proportion examined undeterminable. All but three of the public high schools in the city were included in the 1946 surveys, and one vocational school as well, with participation close to 100 per cent.

Approximately two-thirds of all persons examined in 1946 were white (32,676) and one-third were Negro (15,499). The 2:1 ratio of white to Negro participants in the survey program represented a greater proportion of Negroes than was found in the general population of Baltimore City in which only 20 per cent of the inhabitants were Negro. Of the white people who were examined, 53.5 per cent were males and 46.5 per cent females, among the Negro participants, males constituted 45.3 per cent and females 54.7 per cent. The predominance of males over females among white persons examined and of females over males in the Negro group was due principally to differences in sex distribution in the schools. Sufficient data were not available to determine age distribution for the entire group, but participation of children of elementary school age and younger was discouraged, and elderly people did not participate to any considerable extent. However, despite the policy of discouraging young persons under the age of 15 years from entering into the program, it was found exceedingly difficult to adhere to this in the housing project and community groups and in high schools with lower grade components. If the percentage age distribution of similar groups surveyed in the first half of 1947 is applied to this study, it appears that approximately one-sixth of all persons examined roentgenographically in 1946 were in the age group 10 to 14 years.

#### *Radiographic Reading and Classification of Cases*

Interpretations of the small project films and readings of the follow-up 14 by 17 films were recorded according to a fixed classification. The diagnostic categories for miniature film interpretation were negative, unsatisfactory, defi-

nite tuberculosis, suspected tuberculosis, or nontuberculous disease. Interpretation of the standard 14 by 17 inch celluloid films with respect to the diagnosis of pulmonary tuberculosis followed the National Tuberculosis Association's classification for extent of lesion: minimal, moderately advanced, and far advanced. The U. S. Public Health Service classification plus the reader's judgment were used for designating activity of the lesion: probably active, questionably active, and probably inactive.

All of the small film interpretations represented the impressions of a single examiner, one chest physician who had read all of the survey films since the unit program was initiated. The 14 by 17 film readings were the interpretations of several examiners, although the large majority of them were initially read or later reviewed by the same physician who interpreted the microfilms. There was not the same uniformity of interpretation of the large films because many individuals went to places other than the mobile unit to obtain them. When 14 by 17 films were taken at the city chest clinics, which was a frequent occurrence, the physical and laboratory findings on the clinic history were available to the film reader.

*A case of tuberculosis found by survey* was theoretically defined as one which was so diagnosed on the basis of the miniature and standard size films. The probably active and questionably active groups have, in this inquiry, been considered to constitute the group of clinically significant lesions, the group which would require treatment or observation. The probably inactive group is considered to be one which requires only re-examination with a roentgenogram one year after the survey film.

Final classification and disposition of all individuals whose microfilms had been read as not negative was made after consideration of all available post-survey data. For each person examined roentgenographically in 1946, there had been a post-survey period of observation of at least one year and a maximum of two years for some of them.

*A case of tuberculosis discovered by survey* was defined as one which had not been previously reported, which fulfilled residence requirements, and which had been reviewed and accepted by the Director of the Bureau of Tuberculosis as exhibiting changes in the lungs of tuberculous origin. *Discovered cases* were registered and enumerated in the annual morbidity statistics for the city. The evidence for registration of cases which were believed to require treatment or observation (the "clinically significant" cases) was generally based on history, certain clinical observations, and the roentgenogram and, in addition, one or more of corollary data such as tuberculin reaction, sputum or gastric washing examinations, and blood sedimentation rate. For those cases which were believed to require no more than a single re-examination with a roentgenogram at the end of one year, the "probably inactive" group, the evidence for registration was almost entirely roentgenological, i. e., the appearance on the film of pulmonary changes which were considered consistent with a probably healed tuberculous process.

## RESULTS OF SURVEY PROCEDURE

*Frequency of Pulmonary Tuberculosis in the Total Surveyed Population*

Analysis of the record cards of the 48,175 persons who received chest roentgenograms showed that 47,082 had essentially negative miniature films (97.7 per cent). There were 1,093 persons who had evidence of abnormality of some type or had technically unsatisfactory films. The project film readings of this group of 1,093 "not negative" films (2.3 per cent of the total number done) were as follows:

Unsatisfactory films	60 (0.1 per cent)
Nontuberculous pathology	371 (0.8 per cent)
Tuberculous pathology	662 (1.4 per cent)
Definite tuberculosis	202 (0.4 per cent)
Suspected tuberculosis	460 (1.0 per cent)

With the screening procedure of miniature filming alone, therefore, it was found that approximately one and one-half per cent of all persons examined had definite or suspected evidence of tuberculosis.

All of the persons whose small films showed definite or suspected tuberculosis were asked to return for further examination by means of a full-size film, and 86 per cent responded. Twenty-nine individuals whose microfilms had been interpreted as showing definite tuberculosis and 61 persons whose small films showed suspected tuberculosis did not return for full-size films. In addition to this group of "recalls," roughly one-third of the persons whose miniature films had shown signs of nontuberculous pathology were advised to have 14 by 17 films as it was believed that further roentgenological investigation would be desirable.

Altogether, 755 persons returned for re-examination with 14 by 17 films after initial miniature film screening. Among them, 318 cases of definite or suspected tuberculosis were found, the equivalent of 0.7 per cent of the total number radiographed. The results of their re-examinations are presented in table 1 correlated with the initial project film interpretations. If all persons whose microfilms had been read as "not negative" had been re-examined with 14 by 17 film, and definite or suspected tuberculosis found in the same ratio as presented in table 1, the frequency of these findings in the whole survey group would have approximately 10.8 per cent.

It may be seen that a second radiological examination reduced the tuberculosis findings by approximately one half when comparison is made with the figure of 1.1 per cent based on project film interpretations. Had only one radiological examination been made, twice as many cases of definite or suggestive tuberculosis would have been reported in the mass surveys. In view of recent investigations demonstrating essentially equal intrinsic and extrinsic errors in the interpretation of films of 11 sizes (9, 13), it appears that a second roentgenological examination is not the size of the film used in the re-examination, but is to some considerable modification of initial film interpretation.

The number of cases of definite tuberculosis alone (14 by 17 film readings), exclusive of suspicious cases, represented 0.6 per cent of all persons examined, and the white group (0.7 per cent) and the Negro group (0.5 per cent) were similar. Approximately two-thirds of the definite tuberculous lesions were found to be minimal in extent and only one-third advanced, a finding that has been almost universal in the experience of mass surveys of supposedly healthy individuals. This ratio was exhibited in both the white and Negro population groups in this study.

Among the 292 cases of definite tuberculosis which were found, the extent and probable activity of the lesions were specified in 272 instances (table 2). Almost

TABLE 1

*Correlation of Readings of Project Films and Re-examination by 14 by 17 Films, Mass Surveys, Baltimore, 1946*

	PROJECT FILM IMPRESSION				
	Total	Unsatisfactory	Nontuberculous abnormality	Definite tuberculosis	Suspected tuberculosis
Project films with evidence of pathology or unsatisfactory	1,093	60	371	202	460
Total retakes on 14 by 17 films	755	16	167	173	399
14 by 17 film readings					
Essentially negative	257	15	43	5	194
Nontuberculous abnormality	150	0	112	5	33
Definite tuberculosis	292	1	7	162	122
Minimal	189	1	5	79	104
Moderately advanced	88	0	0	76	12
Far advanced	8	0	0	7	1
Other tuberculosis	7	0	2	0	5
Suspected tuberculosis	56	0	5	1	50

one-half were considered *clinically significant* (0.3 per cent of the total number radiographed), and no essential difference was observed between the white (0.3 per cent) and Negro (0.2 per cent) groups. Approximately one-third of the persons found to have minimal lesions were classified as in need of treatment or observation. These minimal lesions of clinical significance comprised more than half of the total number regarded as clinically significant and 23 per cent of all the tuberculous lesions found. In the combined group of cases read as moderately advanced and far advanced, nearly two-thirds were diagnosed as in need of medical care. These moderately advanced and far advanced cases of clinical significance constituted almost one-half of the total interpreted as of clinical significance and 20 per cent of all the tuberculous cases found.

Most of the differences between white and Negro groups were on the borderline of statistical significance and may have been the result of certain limiting

factors, such as age or the knowledge of race by the film reader. No essential sex differences were noted. Since the age distribution of the total group surveyed was not known, age-specific rates could not be calculated.

*Frequency of Pulmonary Tuberculosis in Constituent Groups Surveyed*

Because the number of apparently healthy persons examined in each of the 50 groups which constituted the surveyed population in 1946 was too small for satisfactory analysis, it appeared advisable to combine comparable groups into larger units. Seven broad constituent groups emerged composed of individuals of similar occupation, place of residence, or place of study. Race distribution

TABLE 2

*Classification of 14 by 17 Films Read as Showing Tuberculosis, according to Extent and Probable Activity of Lesion, 1946*

	ALL RACES		WHITE		NON WHITE	
	Num ber	Per cent	Num ber	Per cent	Num ber	Per cent
Total read as tuberculosis	292		215		77	
Total with probable activity of lesion specified	272	100 0	206	100 0	66	100 0
Clinically significant	125	46 0	88	42 8	37	56 0
Probably inactive	147	54 0	118	57 2	29	44 0
Minimal	180	100 0	135	100 0	45	100 0
Clinically significant	68	37 8	45	33 3	23	51 1
Probably inactive	112	62 2	90	66 7	22	48 9
Moderately advanced and far advanced	91	100 0	71	100 0	20	100 0
Clinically significant	57	62 6	43	60 6	14	70 0
Probably inactive	34	37 4	28	39 4	6	30 0

has been presented for these broad groupings, but sex distribution has not been included since the lack of age data in the material available for analysis placed serious limitations on the interpretations which could be made from sex data alone.

Of the 32,676 white persons who were examined, one-third were high school or junior high school students. Industrial workers, office employees, and department store personnel accounted for another third, and the remaining 30 per cent was made up of residents of housing projects and various communities in the city, college students, and miscellaneous small groups. Of the 15,199 Negro individuals examined roentgenographically, almost one-half were high school or junior high school students. Approximately one-third were drawn from housing projects and different communities in the city, and only a small number were examined at their place of employment.

Comparison among the various survey groups was made with respect to the prevalence of "definite tuberculosis" and the frequency with which clinically

significant tuberculosis" was found, as indicated by the result of interpretation of roentgenographic re-examination (14 by 17 films), and as shown in tables 3 and 4

The percentage of cases of definite tuberculosis found in the various population groups ranged from 0.1 per cent among high school and junior high school pupils to 1.2 per cent among office personnel (table 3). The frequency of finding definite tuberculosis among industrial workers, office workers, department store employees, and residents of various communities was substantially similar and approximately 1.0 per cent. Examination of residents of housing projects yielded

TABLE 3

*Distribution of Cases of Definite Tuberculosis (14 by 17 Film Readings) in Mass Surveys in Baltimore, 1946, according to Constituent Groups and Races*

SURVEY GROUPS	TOTAL			WHITE			NON WHITE		
	Number examined	Definite tuberculosis		Number examined	Definite tuberculosis		Number examined	Definite tuberculosis	
		Num ber	Per cent		Num ber	Per cent		Num ber	Per cent
All groups	48,175	292	0.6	32,676	215	0.7	15,499	77	0.5
Industrial	5,094	57	1.1	3,930	46	1.2	1,164	11	0.9
Business office	5,549	69	1.2	4,565	57	1.2	984	12	1.2
Department store	3,839	38	1.0	3,585	36	1.0	254	2	0.8
Housing project	4,922	28	0.5	2,147	12	0.6	2,775	16	0.6
Community	7,152	63	0.9	4,989	52	1.0	2,163	11	0.5
High School and Junior High School	17,960	19	0.1	10,720	8	0.1	7,240	9*	0.1
College	1,810	6	0.3	1,160	0	0	650	6	0.9
Miscellaneous	1,849	12	0.6	1,580	4	0.3	269	8	3.0

\* Excludes 2 cases in Chinese

0.5 per cent of definite cases, probably a reflection of the high proportion of children examined.

The findings among whites and Negroes were essentially similar for most of the groups. In community surveys, twice as many cases of definite tuberculosis were found among white persons (1.0 per cent) as among Negroes (0.5 per cent), a difference that was probably due to age distribution. Among college students, no cases were found in the white group and 0.9 per cent in the Negro group, the incompleteness of participation of the college students and the fact that the Negro students were almost all females may have accounted for this disparity.

*Tuberculous lesions of clinical significance* were found among all of the constituent groups, except the student groups, with essentially the same frequency (0.3 to 0.5 per cent) and no racial differences were observed. In table 4 are presented the findings for each of the groups.



*Net Contribution to Tuberculosis Case Finding*

To ascertain the full contribution of mass roentgenographic surveys to tuberculosis case finding, it is necessary to add to the cases directly found those which were diagnosed as a result of the follow-up investigations initiated by the survey findings. In addition to the 292 cases of definite tuberculosis found as an immediate result of the surveys, there were 35 cases similarly diagnosed as a result of later examinations. A total of 327 cases of tuberculosis, therefore, was the gross contribution of mass radiography in 1946.

To determine the role of mass surveys in the *discovery of new cases* of tuberculosis in Baltimore, the 327 found cases were subjected to the requirements for

TABLE 4

*Distribution of Cases of Clinically Significant Tuberculosis (14 by 17 Film Readings) in Mass Surveys in Baltimore, 1946, according to Constituent Groups and Races*

SURVEY GROUPS	TOTAL			WHITE			NON WHITE		
	Number examined	Clinically significant tuberculosis		Number examined	Clinically significant tuberculosis		Number examined	Clinically significant tuberculosis	
		Number	Per cent		Number	Per cent		Number	Per cent
All groups	48,175	125	0.3	32,676	88	0.3	15,499	37	0.2
Industrial	5,094	21	0.4	3,930	16	0.4	1,164	5	0.4
Business office	5,549	21	0.4	4,563	18	0.4	984	3	0.3
Department store	3,839	20	0.5	3,585	19	0.5	254	1	0.4
Housing project	4,922	15	0.3	2,147	7	0.3	2,775	8	0.3
Community	7,152	22	0.3	4,989	17	0.3	2,163	5	0.2
High School and Junior High School	17,960	17	0.1	10,720	8	0.1	7,240	7*	0.1
College	1,810	3	0.2	1,160	0	0	650	3	0.5
Miscellaneous	1,819	6	0.3	1,580	3	0.1	269	3	1.1

\* Excludes 2 cases in Chinese

registration and the result is shown in table 5. Twenty-one of the cases were excluded because the diagnosis of tuberculosis was later withdrawn, 26 were excluded because of nonresidence in Baltimore City, and 70 were already known to the health department. The resultant net yield of discovered cases was 210, or 0.4 per cent of the 48,175 examinees. Approximately one-half of the discovered cases (99) were considered clinically significant, 0.2 per cent of the total number subjected to roentgenographic examination.

Minimal lesions formed more than two-thirds of all the new cases, but only one-third of the minimal lesions were considered of clinical significance. That is to say, cases of minimal tuberculosis requiring treatment or observation constituted approximately one-fourth of all discovered cases. Moderately advanced and far advanced lesions of clinical significance were discovered to substantially the same extent as the clinically significant minimal lesions.

*Ratio of "discovered" cases to "all reported" cases* In table 6 are shown the number and type of cases of pulmonary tuberculosis discovered by mass sur-

TABLE 5

*Cases of Definite Tuberculosis (including Clinically Significant and Inactive) Discovered as a Result of Mass Surveys in Baltimore in 1946, All Races*

CLASSIFICATION	TOTAL NUMBER FOUND	NUMBER DIAGNOSIS REVISED	NUMBER NOT RESIDENT	NUMBER PREVIOUSLY REPORTED	DISCOVERED CASES		
					Total number discovered	Number clinically significant	Number probably active
All types	327	21	26	70	210	99	111
Minimal	214	13	18	40	143	50	93
Moderately advanced	94	2	8	27	57	40	17
Far advanced	10	1	0	2	7	6	1
Primary (other)	9	5	0	1	3	3	0

TABLE 6

*Ratio of Cases Discovered by Survey to all Reported Cases of Pulmonary Tuberculosis in Baltimore in the Year 1946*

CLASSIFICATION OF LESIONS	TOTAL NUM- BER RE- PORTED	NUM- BER OF TOTAL RE- PORTED BY SUR- VEYS	PER CENT OF TOTAL RE- PORTED BY SUR- VEYS	WHITE			NON WHITE		
				Num- ber re- ported	Num- ber of total re- ported by surveys	Per- cent of total re- ported by surveys	Num- ber re- ported	Num- ber of total re- ported by surveys	Per- cent of total re- ported by surveys
All cases with extent of lesion classified	1,465*	210	14.3	865	148	17.1	600	60	10.0
Minimal All types	503	143†	28.5	354	99	28.0	149	43	29.0
Active	202	50†	24.7	135	25	18.5	67	24	36.0
Inactive	258	93	36.0	209	74	35.4	49	19	39.0
Pleural effusion	43			10			33		
Moderately and far ad- vanced All types	849	64†	7.5	482	49	10.0	367	14	3.8
Severe primary lesions	78	3	4.0	18			60	3	5.0
Acute miliary or disseminated	35			11			24		

\* Excludes 3 pulmonary cases with extent of disease and activity unspecified

† Includes 1 case in Chinese

veys in 1946 in relation to the entire year's morbidity notification from all sources

In Baltimore in 1946, the diagnosis of pulmonary tuberculosis was accepted in 1,468 cases, including those discovered by survey. Minimal lesions of all types comprised 34 per cent of all reported pulmonary cases. Minimal lesions

designated as active (corresponding to the study classification of clinically significant) were reported in only 13.8 per cent of all new cases. Moderately advanced and far advanced cases in all stages of activity constituted 58 per cent of all notifications.

The 210 cases discovered by mass surveys contributed 14.3 per cent towards the total pulmonary cases reported.

In the group of active minimal cases, one-fourth (50) of the total number reported were the product of survey examinations. This represented a contribution of 18.5 per cent to the active minimal cases reported in white persons and more than one-third towards the total number of cases of active minimal tuberculosis in Negroes. Although the yield of 50 cases of clinically significant minimal tuberculosis from the examination of 48,175 individuals appears exceedingly small, the reporting of this type from all other sources in Baltimore was so slight as to make the survey contribution a considerable one.

Advanced cases of all types which were discovered by survey formed only 7.5 per cent of the year's reported cases in this classification.

It was not possible to thoroughly investigate the discovered cases to determine how many of them could have been reported through other channels, had these other channels functioned more efficiently. However, a superficial investigation was made of one-half of the 99 discovered cases of clinical significance. It was found that 5 of the clinically significant discovered cases were contacts of active or fatal cases known to the health department (3 minimal and 2 moderately advanced); these cases could have been found by methods other than survey, such as more intensive nursing and clinic follow-up. There were in addition 5 cases which were known to hospital dispensaries or private physicians but had never been reported to the official agency. These cases could have been known to the health department without benefit of survey only if reporting by private physicians and general hospitals were improved.

On the basis of these incomplete data, it appears that approximately 10 per cent of the discovered cases of clinical significance could have been found by improved contact examinations, and 10 per cent were already under the supervision of private physicians or hospitals, although unknown to the health department.

It would be of considerable interest to examine the reported cases of respiratory tuberculosis in former years in Baltimore to determine whether there had been a change in the ratio of early to advanced cases since the advent of mass radiography of supposedly healthy individuals. Unfortunately, the tuberculosis morbidity statistics before the year 1913 do not include a description of extent and probable activity of tuberculous lesions. A review of the five-year period, 1913-1917, however, can offer some points of interest.

The period 1913-1917 was one of continuous tuberculosis case finding by means of mass radiography. In 1913 the activities of the military induction stations in Baltimore were at their height and all cases of tuberculosis found in persons examined for military service were reported to the Baltimore City Health Department. In 1914, while military examinations were continuing at a

good pace, the mobile photoroentgen unit of the Baltimore City Health Department went into operation and by 1945, when reports from the induction stations were diminishing, the results of the mobile unit's activity were becoming apparent

In 1944, the number of persons examined by the induction centers plus those examined by the mobile unit equalled the number examined for military service in 1943. During the subsequent three years, almost all radiography was done by the mobile unit (examinations for military service ceased in October 1946) and the number of persons examined in each of the three years was greater than during 1943 or 1944.

Nevertheless, the number of reported cases of active minimal tuberculosis, which had been high in 1943 and at its peak in 1944, declined sharply after 1944, and the ratio of reported active minimal cases to advanced cases declined in

TABLE 7

*Ratio of Reported Cases of Active Minimal Tuberculosis to Reported Cases of Advanced Tuberculosis, all Types, Baltimore, 1943-1947*

YEAR	TOTAL			WHITE			NON WHITE		
	Number minimal tuberculosis active	Number advanced tuberculosis all types	Ratio of active minimal to advanced All types	Number minimal tuberculosis active	Number advanced tuberculosis all types	Ratio of active minimal to advanced All types	Number minimal tuberculosis active	Number advanced tuberculosis all types	Ratio of active minimal to advanced All types
1943	322	1,070	0.30	191	596	0.32	131	474	0.28
1944	378	961	0.39	242	542	0.45	136	419	0.32
1945	228	936	0.24	151	561	0.27	77	375	0.20
1946	202	849	0.24	135	482	0.28	67	367	0.18
1947	157	894	0.18	95	485	0.19	62	409	0.15

parallel fashion. This is illustrated in table 7 for the white and Negro populations of Baltimore. During the same five-year period, deaths from pulmonary tuberculosis decreased among white residents but Negroes experienced no essential change.

It appears that mass radiography, as practiced in Baltimore by the mobile unit, did not uncover as many cases of active minimal tuberculosis as did the compulsory and complete screening of an adult male group of the population, selected only with respect to age. Although large numbers were examined by the mobile unit, groups which are generally found to have a high tuberculosis rate, such as unemployed and homeless men (who were compelled to be examined by the induction stations), were not systematically included, and, on the other hand, many children participated and they were found to have very little tuberculosis.

The yield of the mobile unit's activities in finding active minimal tuberculosis appears also to have diminished during the three and one-half years of its operation. The repetition of surveys of certain groups, four groups in 1946 and almost a dozen in 1947, probably diminishes the returns of case finding if the groups are fairly stable and those re-examined are the same people.

*Disposition of Discovered Cases of Tuberculosis*

Information concerning the provision of medical care for the newly discovered cases was gathered from the files of the Baltimore City Health Department for the maximum post-survey observation period possible in this inquiry, the twenty-four months from January 1946 to December 1947. The absence of follow-up data in the health department records did not necessarily mean that no further examinations had been made but rather that further observations were not known to the health department.

TABLE 8

*Follow-up Observations of Cases of Pulmonary Tuberculosis Discovered in Mass Surveys in Baltimore in 1946 during a Two year Post-survey Period*

	TOTAL				WHITE				NON WHITE			
	All cases	Minimal clinically significant	Minimal inactive	Advanced all types	All cases	Minimal clinically significant	Minimal inactive	Advanced, all types	All cases	Minimal clinically significant	Minimal inactive	Advanced all types
Number discovered cases	210	49	93	63	148	25	74	49	57*	24	19	14
Number having some follow-up	112	40	31	41	68	18	23	27	44	22	8	11
Number having follow-up 1 year or more	89	32	24	33	52	14	18	20	37	18	6	13
Number found active at any time	32	6	3	21	13	1	2	10	17	5	1	11
Number hospitalized	32	13	2	15	12	4	1	7	17†	9	1	7
Number of deaths	4			4	1			1	2‡			2

\* Excludes 3 cases of primary tuberculosis in Negroes and 2 cases of pulmonary tuberculosis in Chinese

† Excludes 2 cases of primary tuberculosis in Negroes and 2 cases of pulmonary tuberculosis in Chinese

‡ Excludes 1 case in Chinese

Total includes 3 cases of primary tuberculosis in Negroes and 2 cases of pulmonary tuberculosis in Chinese

A summary of the follow-up observations during 1946-1947 on the cases of tuberculosis discovered by the survey method is shown in table 8.

Of the 210 discovered cases, 98 cases, or 46 per cent, were not known to have had follow-up examinations after survey. Most of these had been originally classified as inactive. Of the 18 clinically significant cases without recorded follow-up observations, the majority were said to be under the care of private physicians. The only definite information which could be presumed about cases without known subsequent examinations was that they did not enter a sanatorium or die of tuberculosis in Maryland.

In describing the post-survey condition of the 112 cases who had follow-up examinations, certain definitions and assumptions have been made. Because of lack of uniformity in follow-up data and because of the paucity of cases in certain classifications, two broad classifications of condition after survey have been set up. *Active* includes all cases so described, all cases showing progression, all hospitalized cases for whom activity status was not known, and all fatal cases. *Inactive* includes all findings so described, all examinations which were said to show no change, and all findings which were said to show regression or clearing of lesions (although any change represents activity, the direction in these cases was towards improvement and they were, therefore, included with the "favorable" cases).

Of the 112 cases which had some follow-up, there were 31 which were found to be active at some time during the post-survey observation period, and in almost each case this decision was reached within six months after the survey film was taken.

The infrequency with which minimal lesions diagnosed as clinically significant were later found to show evidence of activity is noted. In fact, there appears to be no noteworthy difference between the proportion of active cases resulting from those originally called clinically significant and those initially diagnosed as probably inactive. However, considering the fact that the "no follow-up" group consisted largely of cases called inactive, and the "follow-up" group contained a majority of clinically significant cases, the lack of difference might not have been so apparent if the "no follow-up" group could have been included.

The seeming innocuousness in white persons of minimal lesions which appear to be roentgenologically clinically significant is quite interesting. Only one of the 18 clinically significant minimal cases which had follow-up later showed signs of activity. The proportion was considerably higher among Negroes, but even in this group only 5 out of the 22 clinically significant minimal cases in Negroes showed evidence of activity.

*Hospitalization.* One of the problems frequently mentioned in connection with mass radiography programs is the difficulty of providing institutional care for the tuberculosis cases which would be uncovered, particularly in areas where sanatorium facilities are inadequate, as in the state of Maryland.

The follow-up records of the cases of tuberculosis found by survey in 1946 show that 32 of the 210 newly discovered cases and 12 of the 70 previously known cases were hospitalized at some time during 1946 and 1947. The addition of 44 cases to the sanatorium load of Baltimore City over a period of two years does not indicate that survey activities as conducted by the Baltimore City Health Department produced a problem of hospitalization of serious proportions.

One year after survey, two-thirds as many Negroes who had been discovered to have lesions requiring treatment or observation had been hospitalized (45 per cent) as had white persons in similar condition. One white person and one Negro whose pulmonary lesions were regarded as inactive were hospitalized seven to eight months after survey.

*Deaths* There were 5 persons found by survey to have tuberculosis during the year of 1946 who succumbed to the disease before the end of 1947. Two of the fatal cases were white, 2 were Negro, and one was Chinese. All had advanced pulmonary disease when first examined. Four of the 5 cases were newly discovered, one was already known to the health department.

#### DISCUSSION AND SUMMARY

This analysis of the experience of the Baltimore City Health Department with the application of mass radiography to some fifty groups of the population, constituting 48,175 apparently healthy persons, or about 5 per cent of the population, has revealed a net yield of tuberculosis cases which appears quite modest in relation to the effort expended. From an epidemiological viewpoint, the effectiveness of this part of Baltimore's tuberculosis-control program can be measured not by the number of individuals whose films showed evidence of tuberculous lesions but by the number of individuals who were discovered to have lesions which were of clinical significance, requiring medical supervision and care.

In the material which has been analyzed, it is interesting to note the manner in which the number of persons classified as having "definite or suspected" tuberculosis as a result of the reading of miniature films decreased through successive steps in the screening process. Re-examination by large film of all those who could be persuaded to return (86 per cent) reduced the number from 662 to 292 as having evidence of definite tuberculosis, and of these only 125 were thought to have lesions which were of clinical significance. When, however, these individuals were further processed, taking into consideration other clinical evidence and eliminating those who were nonresidents or had been previously reported, the number of cases remaining which were classified as having tuberculosis was 210, and of these 99 were thought to have an active disease process. Of the 210, the health department was successful in following 89 for a year or more. There were only 32 which were found to have unquestioned clinical activity, almost all of whom were hospitalized, and 1 of whom died. An unknown additional number were under private care.

As was stated in the introduction, one of the primary objectives of mass roentgenographic examinations is to increase the proportion of cases discovered in the minimal stage which are of clinical significance. The net yield in this respect was somewhat disappointing. Out of 1,468 cases of pulmonary tuberculosis which came to official attention during the year, only 202 were classified as active minimal, and of this latter number approximately one fourth were contributed as a result of survey activity. That is to say, in spite of considerable effort expended in mass surveys, the proportion of new cases which were discovered in the active minimal stage was not materially increased. It may be that rather meager results are to be expected, since the screening process begins with a single microfilm observation on a single day on each individual. A film that was negative on this occasion might have been positive several weeks later. Moreover, the significance of minimal lesions thought to be active because of

roentgenographic appearance still remains to be elucidated. The development of better diagnostic techniques than are now available is needed before those lesions that are important from the point of view of possible progression can be definitely separated from those that are unimportant and will regress spontaneously without medical care.

The effort to find population groups which were contributing unusually to the tuberculosis problem of the community was unsuccessful. In fact, so far as could be judged from the data available, the frequency of positive findings was surprisingly similar in all of the adult groups which were surveyed. The only significant differences noted were the lower rates which were found in the school groups which were composed largely of adolescents. Only crude comparisons could be made, however, because age-sex specific rates could not be calculated. The obvious effect of selection makes the use of prevalence rates obtained in these survey groups unreliable as a basis for estimating the prevalence of the disease in the city as a whole.

Whether or not mass roentgenographic examinations of *all* kinds of groups of apparently healthy persons who can be easily and readily assembled should be continued remains to be determined. One possible modification of policy is to concentrate this effort more completely on *adult* groups living and working in the poorer and more crowded sections of the city, and especially to seek out adult Negro groups. While the prevalence in the two races is much the same, the significance of discovery of cases among Negroes differs from that of similar findings among whites since Negroes display the most pronounced tendency towards rapid, fatal progression of tuberculous lesions.

It also remains to be determined whether, in a community where tuberculosis is a major problem, an intensification of the search for new cases among the household associates and social and occupational contacts of known open cases may not yield a greater return for effort expended. A very superficial investigation in the course of this study revealed the fact that at least 10 per cent of the cases discovered by survey might have come to attention through other channels.

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# THE SUITABLE DOSE OF TUBERCULIN FOR SINGLE TEST TUBERCULIN TESTING<sup>1</sup>

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## INTRODUCTION

Tuberculin has long been used in two doses for testing purposes and those who do not react to the second dose are considered to be uninfected with the tubercle bacillus. Recently, evidence has been shown by those working in this field that there are very likely some factors causing nonspecific reaction when a too large dose of tuberculin is used. This hypothesis of nonspecific reaction is supported by Furecolog, Hewell, Nelson, and Palmer's well planned experiment (1) in which they found that the dose five times the first dose (1 T U<sup>2</sup>) used in the traditional two-dose tuberculin testing is sufficient for all purposes of diagnosing tuberculous infection, and nonspecific reactions are liable to be elicited with larger doses. Seibert also holds the same opinion (2). Hsueh and Ch'iu in 1941 showed that 0.00025 mg. of PPD (12.5 T U) could be safely used for single dose testing (3). Apparently European workers are of similar opinion for the WHO-ICEF recommendation (4) of the final dose of tuberculin for pre-BCG tuberculin testing is to be 10 T U.

The present report deals with a comparison of results with 10, 50, 100, and 250 T U in Chinese children to find out the most suitable dose of tuberculin that can be used for single dose testing.

## MATERIAL AND METHOD

As nearly all the people above the age of twenty years of age in this city are infected with the tubercle bacillus, school children were selected as the test population. The total number of children tested was 5,512, aged between four and sixteen years, students at ten primary schools in the First Health District of Peiping. The tuberculin used was PPD, a commercial product of Parke, Davis and Co. It was used according to the manufacturer's direction without further standardization. The doses used were as follows:

0.000,02 mg	1 T U
0.000,2 mg	10 T U
0.001 mg	50 T U
0.002 mg	100 T U
0.005 mg	250 T U
all in 0.1 cc. solution	

All the children were first tested with 1 T U. Those who did not react were given a second test with the other four doses injected at one sitting. The first dose was injected on the middle portion of the flexor surface of the left forearm.

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<sup>2</sup> T U = Tuberculin unit. 1 T U = 1/100 mg. of O.T., or 0.000,02 mg. of PPD.

The four doses of the second test were injected on the flexor surface of both forearms, with 10 and 250 T U on the left and 50 and 100 T U on the right. The two injections on one arm were made three inches apart. The results were read at the end of forty-eight hours, the criteria being as follows:

Induration	Result
5 to 10 mm	+
10 to 20 mm	++
20 mm and over	+++
Ulcer or blister	++++

TABLE 1  
Number of Reactors to Various Doses of the Second Test

AGE	SECOND TEST																						
	10 T U					50 T U					100 T U					250 T U					Number of reactors to second test	10/250 T U	
	+	++	+++	++++	Total	+	++	+++	++++	Total	+	++	+++	++++	Total	+	++	+++	++++	Total			
4																							
5	3				3	1	2			3	1	1			2	1	1	2		4	4	75	0
6	17	1			18	15	7			22	16	10	2		28	14	10	5		29	29	62	1
7	29	15			44	11	31	6		48	14	30	11		55	25	15	28		68	68	64	7
8	45	23	1		69	24	44	10		78	22	43	23		90	23	33	39		95	95	72	7
9	61	16	2		77	33	44	12		89	32	59	25		100	16	38	45		99	100	77	8
10	56	23	3		82	32	46	18		96	16	61	28		103	18	52	42		112	112	73	2
11	50	30	4		92	26	65	17		108	27	51	32	1	121	29	43	57	1	130	130	70	7
12	57	22	5		84	20	53	22		95	5	36	39		95	9	36	55		100	100	84	0
13	59	23	4		86	12	40	19		71	8	3	29		73	7	24	44		75	75	88	0
14	4	3			7	3	2	3		8	1		4		8	1	3	5		9	9	77	8
15	4				4	1	1			2	1		1		2	1		1		2	4	—	
16																							
Total	373	156	19		548	174	332	168		620	139	339	192	1	677	141	254	321	1	723	726	75	8

Only induration was measured, redness without induration was not considered as significant. All readings were made with extreme care to avoid any possible false reaction.

#### RESULTS

Of the 5,512 children tested with 1 T U, 2,100 did not react to it. These nonreactors were further tested with four doses of 10, 50, 100, and 250 T U. The number of reactors to the various doses are shown in table 1.

Among the 2,941 who received the second test, there were 548, 620, 677, and 723 who reacted to 10, 50, 100, and 250 T U, respectively. If the number of

reactors to 250 T U is considered to be 100 per cent of those who would react to tuberculin, then the 10, 50, and 100 T U doses are capable of eliciting 75.8, 85.7, and 93.6 per cent of reactors, respectively.

Since the figures in table 1 only represent the results obtained from the non-reactors to the first test, it is more rational, in comparing the results of 10, 50, 100, and 250 T U, to add the number of reactors to the first test to the numbers of reactors in table 1.

TABLE 2  
*Accumulated Number of Reactors to the Various Doses*

AGE	TOTAL NUM BER TESTED	REACTORS TO VARIOUS DOSES										
		1 T U		10 T U		50 T U		100 T U		250 T U		10/250 T U per cent
		num ber	per cent	num ber	per cent	num ber	per cent	num ber	per cent	num- ber	per cent	
4	2	1	—	1	—	1	—	1	—	1	—	—
5	39	10	—	13	—	13	—	12	—	14	—	—
6	432	129	29.9	147	34.0	151	35.0	157	36.2	158	36.6	93.0
7	656	253	38.6	279	42.5	301	45.9	308	47.0	321	48.9	86.9
8	859	344	40.0	413	48.1	422	49.2	434	50.5	439	52.3	94.1
9	734	352	48.2	429	58.5	441	60.1	452	61.5	451	61.4	95.1
10	861	434	50.5	516	59.9	530	61.5	537	62.2	546	63.4	94.5
11	778	429	55.2	521	67.0	537	69.0	550	70.7	559	71.9	93.1
12	599	371	61.9	455	76.0	466	77.8	466	77.8	471	78.6	96.5
13	405	253	62.5	319	76.3	324	80.0	326	80.5	328	81.0	97.2
14	129	97	75.2	104	80.6	105	81.4	105	81.4	106	82.2	98.1
15	16	11	—	15	—	13	—	13	—	13	—	—
16	2	2	—	2	—	2	—	2	—	2	—	—
Total	5,512	2,686	48.9	3,214	58.3	3,306	60.0	3,363	61.1	3,409	61.8	94.3

From table 2 it is shown that among the 5,512 children tested, 3,214 reacted to 10 T U while 3,306, 3,363, and 3,409 reacted to 50, 100, and 250 T U, respectively, which means that the 10, 50, and 100 T U doses can yield 94.3, 97.0, and 98.7 per cent of reactors as compared with the number of reactors to 250 T U.

#### DISCUSSION

In epidemiological work the two-dose tuberculin testing has been found to be very inconvenient. This inconvenience can be eliminated if a suitable dose of tuberculin can be found which, when used as a single test, can yield enough significant reactors without causing too many severe reactions. As it is known that the first strength (1 T U) used in the two-test tuberculin testing can yield only about 50 per cent reactors and a certain number of nonspecific reactions are elicited by the traditional second strength (250 T U), the suitable dose of tuberculin for a single test must lie between one and 250 T U. As shown by the data in table 2, 10 T U are capable of yielding 94.3 per cent of all reactors to

250 T U and causing probably no more than 4.6 per cent of severe reactions (++++) (3), though 50 and 100 T U can yield a few more reactors, they are statistically nonsignificant and even less desirable when nonspecific reactions are taken into account. The difference between numbers of reactors to 10 and 250 T U is so small that it is only barely significant, and in two-test tuberculin testing there will be 50 per cent nonreactors to the first test who have to receive a second test of 250 T U (in Denmark 100 T U). The average amount of tuberculin used on each person will be around 125 T U. In epidemiological work the material and time thus saved would be quite considerable. So it is our opinion that 10 T U can be considered as the suitable dose of tuberculin for single-dose tuberculin testing.

#### SUMMARY

1. An experiment to find out the suitable dose of tuberculin for single-test tuberculin testing was made in a test population consisting of 5,512 primary school children between four and sixteen years of age.

2. Ten T U of tuberculin (PPD tablets) were found to be capable of yielding 94.3 per cent of all possible reactors to 250 T U and can be recommended as the suitable dose of tuberculin for single-test tuberculin testing.

#### SUMARIO

##### *La Dosis Adecuada de Tuberculina para la Comprobación con Reacción Única*

1. Este experimento tenía por objeto descubrir la dosis adecuada para la comprobación con tuberculina en una sola reacción.

2. La población comprobada constaba de 5,512 alumnos de las escuelas primarias, de 4 a 16 años de edad.

3. Diez Unidades de Tuberculina resultaron suficientes para descubrir 94.3 por ciento de todos los posibles reactores a 250 Unidades de Tuberculina, de modo que puede recomendarse esa dosis como adecuada para una sola comprobación con tuberculina.

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pected cases, early in 1928 a routine fluoroscopic examination became a part of the annual physical examination of every home office employee. A chest roentgenogram was obtained if an employee had suggestive findings by fluoroscopy, significant symptoms, abnormal physical signs, or history of tuberculous contact. Furthermore, he was kept under close medical supervision which included repeated roentgenograms.

As soon as fluoroscopic examinations were started as a routine procedure, cases were detected which had roentgenological evidence of what once must have been disease of considerable extent and probably tuberculous in character but, upon discovery, had the appearance of a well-stabilized process. A less familiar type of lesion was also discovered, a small circumscribed homogeneous hazy or mottled area of an entirely different character than those just described. In addition, as would be anticipated, lesions of an unquestionably dangerous nature were also found. Even in the beginning it was believed that any abnormal finding on the chest roentgenogram should not be dismissed lightly, but it seemed probable that not every person under consideration needed treatment. In many instances it was perplexing to know when it was safe to wait for the development of further evidence and information, and when it was unsafe to wait.

During the first few years of routine fluoroscopy at the annual examination of employees, 139 had chest roentgenograms which were classified as apparently arrested tuberculosis (males, 87, females, 52) minimal, 120, advanced, 19. These were found among apparently healthy people at work, practically all of whom had been with the company since leaving school. Nevertheless, after close questioning and careful examination the examiners were convinced that these individuals had not been aware of any serious or prolonged illness and their records showed that they had not been away from work for any length of time. Especially noteworthy was the absence of symptoms, physical signs, or positive laboratory evidence to account for or to corroborate the fluoroscopic and roentgenographic findings. The need for new criteria to determine the correct disposition of these cases was immediately apparent. As these persons were observed and experience increased, it became apparent that some of them had been able to resist a tuberculous involvement without being "sick" in the usual sense of the word. Moreover, some persons whose first roentgenograms showed a small hazy or mottled area remained well and the lesion cleared rather promptly during the period of observation, while others, in time, proved to have active progressive tuberculosis. These observations raised the question whether it might be possible to predetermine which cases ultimately would do well or badly and which needed a relatively short period of careful observation to determine the trend.

As the case-finding work progressed, a routine system for studying each individual and recording the findings was developed and more was learned about the pitfalls in the problem of disposition. When a roentgenogram disclosed a lesion the employee was questioned carefully about his family and personal history, particularly in regard to the possibility of tuberculous contact. A physical examination was made by a trained chest specialist,<sup>2</sup> the sputum, if present, was

<sup>2</sup> Dr. Ada Chree Reid has carried out the advisory and supervisory clinical work referred to among home office employees.

examined, and during the period of evaluation roentgenograms were repeated at short intervals. It was unusual to find tubercle bacilli since only a few persons had expectoration and refinements of examination in general use today were unknown or unavailable when the majority of the cases were detected. It was soon learned that little diagnostic or prognostic importance could be attached to fluctuations in body weight. Active and newly developing lesions were found in employees, some of whom were gaining and some losing weight, and such changes were disregarded. It became apparent, too, that age, sex, weight, absence of physical signs, negative laboratory reports, and most symptoms were generally of little help in determining disposition. Consequently more and more reliance was placed on roentgenographic findings. Experience with employees treated at the sanatorium at Mount McGregor since 1914 had revealed that patients with minimal lesions fared much better from the standpoint of morbidity and mortality than those with advanced disease, but this knowledge was not particularly helpful in itself. Some of the lesions which seemed to be well stabilized and proved to be relatively insignificant were advanced in extent, and some of the lesions which were small upon detection proved to be, or progressed into, active tuberculous disease.

After all reports were assembled, a clinical recommendation was made to the employee (1) to continue at work and follow all normal activities during careful periodic medical observation and supervision, or (2) to continue at work temporarily while undergoing special studies, usually with activity restricted, or (3) to enter a hospital or sanatorium immediately.

If sanatorium care was indicated, it was available at the company sanatorium at Mount McGregor without cost to the employee. While in the sanatorium the employee not only received care and treatment, but disability benefits to which he was entitled under his group insurance contract. He knew too that he would be re-employed upon successful completion of cure. If sanatorium treatment did not seem to be indicated at once, the employee continued at work under medical supervision by Doctor Reid, thus permitting the acquisition of further information and the evaluation of all the evidence before making a final decision.

In many cases it was found difficult to convince an employee, his family, or his private physician of the necessity for sanatorium treatment or medical supervision when the decision was based largely on roentgenographic findings. As a matter of fact, the first case of this type admitted to the sanatorium at Mount McGregor caused some consternation to the staff because it could not be diagnosed at that time as a case of pulmonary tuberculosis according to the Sanatorium Association and National Tuberculosis Association classification, despite the fact that no other diagnosis seemed tenable.

It is well known that an acceptable classification of the *extent*<sup>3</sup> of involvement has been available and has been in general use for years. But a satisfactory classification of the *character* of the lesion has not been adopted for many reasons,

<sup>3</sup> "Extent" of pulmonary lesions (minimal, moderately advanced, far advanced) as defined in the Diagnostic Standards and Classification of Tuberculosis of the National Tuberculosis Association.



although physicians caring for tuberculous patients routinely evaluate this feature. There have been marked differences in appraisal, terminology, and judgment in interpretation, and attempts to read pathological characteristics and implications into the wide variety of densities and shadow patterns have added

TABLE 1  
*Roentgenographic Classification and Insurability*

CLASSIFICATION OF LESION BY ROENTGENO- GRAM	ROENTGENOGRAPHIC APPEARANCE	RECOMMENDATION
Inactive	Extent Any minimal or moderately advanced (N T A ) Character Fine or coarse strands, small or large calcific densities, small opaque areas with borders clearly outlined. May be localized or scattered. <i>No cavities present</i>	Insurable
Active	1 Extent Minimal (N T A ) Character Areas of cloudy mottling or homogeneous densities, borders hazy or not clearly defined. No suggestion of cavity	Uninsurable
	2 Extent Moderately advanced (N T A ) Character Areas of cloudy mottling or homogeneous densities, borders hazy or not clearly defined, cavitation not in excess of 4 cm. in diameter	Uninsurable
	3 Extent All far advanced (N T A )	Because of the recognized heavy mortality in the far advanced group, all such cases were classed as active, i.e., uninsurable

to the confusion. These and other difficulties have no doubt delayed the acceptance and inclusion of the *character* of a lesion into a useful and workable classification.

Necessity, however, forced the development of a system of consistent appraisal of roentgenograms submitted by applicants for life insurance in whom there was a question of pulmonary tuberculosis. When a person applies for life insurance a decision to insure or not to insure must be made, there is no middle ground.

Therefore, in 1930 a classification for roentgenograms of the chests of applicants for insurance was adopted and three descriptive categories were used: (a) average healthy chest, i.e., no evidence of disease, insurable, (b) inactive tuberculosis, insurable (table 1), and (c) active tuberculosis, uninsurable (table 2).

Inevitably there are some films which fall somewhere between the arbitrary divisions b and c. In such instances, the examiners used their best judgment as to whether the appearance seemed to be more or less favorable and made a decision as to insurability in each case.

*Identification of Evidence of Value in Prognosis*

Although a *modus operandi* for employees, applicants for employment, and applicants for life insurance, had been developed, the question arose whether it

TABLE 2  
*Description of Lesion, Age, Sex, and Disposition at Diagnosis of Pulmonary Tuberculosis*

SEX	CHARACTER OF LESION BY ROENTGENOGRAM* AGE	TOTAL	DISPOSITION	
			Continued at Work	Began to Cure
Total		592	308	284
Males		206	147	59
Inactive				
Under age 35		32	25	7
Age 35 or over		68	67	1
Questionably active				
Under age 35		37	16	21
Age 35 or over		39	34	5
Active				
Under age 35		25	4	21
Age 35 or over		5	1	4
Females		386	161	225
Inactive				
Under age 25		35	17	18
Age 25 or over		69	60	9
Questionably active				
Under age 25		143	41	102
Age 25 or over		82	38	44
Active				
Under age 25		43	4	39
Age 25 or over		14	1	13

\* See Table 6

was possible to find and identify evidence that would indicate what type of newly found lesions would do well or would do badly. If this were possible, it would be invaluable in the perplexing question of disposition. It is believed that this report on the analysis of the experience with this group of employees and applicants for life insurance gives a workable answer.

The clinical program among home office employees was carried out by Dr Reid and has been described fully elsewhere (1, 2). The disposition of each case was made and carried out in accordance with conservative clinical judgment. Some employees continued at work, some began to cure, and at a later date a

few died. So far this is simply the usual story of any large group of tuberculous people followed for a long period of years.

The importance of the present report, however, is in the relationship between the clinical course and outcome, and the classification of the original chest roentgenogram. Two of the writers (J A E and H H F) independently classified the initial film without reference to the medical chart and without knowledge of the clinical aspects of the case. There was an agreement of classification between these two examiners of over 90 per cent. In all cases of original disagreement a conference resulted in a classification by agreement. There has been considerable recent discussion and question of the ability of roentgenologists to agree either with themselves or with others on classification, but without entering this discussion the writers are reporting their own experience.

After the roentgenograms were classified and after the clinical course was well established, the correlations and statistical analyses were made (M G S). A special study card was prepared for each case showing the initial findings, the course, and outcome chronologically. The changes evident by serial roentgenographic examinations, *i e*, softening or hardening, increase or decrease, or stability, were plotted by one of the writers (H H F). The clinical data (which had been entered on the medical chart whenever the patient was seen) were summarized and transferred to the study card strictly according to rules previously prepared. Thus the progress of each individual could be visualized at a glance. Statistical analyses were made of the relationship between the various factors. It cannot be emphasized too strongly that this compilation and analysis of the material was made objectively. Judgment concerning the lesions on the roentgenogram and selection of the pertinent clinical data were not modified by hindsight or by knowledge of the final outcome of the case.

*Employee group.* The employee group is made up of 592 Metropolitan Life Insurance Company personnel whose lung lesions were discovered under the program of tuberculosis detection and control. None had a previous history of tuberculosis, 99 had had a previous roentgenographic examination considered negative for tuberculosis, and 493 had had no previous roentgenogram of the chest. After detection, all were under medical supervision by Dr A C Reid from one to twenty years and had repeated roentgenographic examinations.

The factors studied include character and extent of the initial lesion, physical signs, symptoms, weight, sex, age, and disposition at time of diagnosis. The follow-up observations include interval changes in the roentgenographic appearance, *i e*, softening or hardening, increase or decrease, or stability, status of the employee, *i e*, whether at work or able to work, curing, or dead, continued or subsequent signs, symptoms, or changes in weight, and surgical procedures for tuberculosis.

## RESULTS

In the first analyses the material was divided into five-year age groups and subdivided by sex and roentgenographic classification. These groups varied so in size (from one case to 123 cases) that no valid conclusions could be drawn. It was

noted, however, that in general the younger people had a poorer outcome than the older people. Therefore, the material for each sex was divided into two halves. This resulted in groupings of males under age 35, and age 35 or over, at the time of the initial roentgenogram, and for females under age 25, and age 25 or over. The designation of younger and older groups in the subsequent discussion is used for these divisions. The ratio of males to females or the ratio of younger to older people has no significance because the age distribution of the employee group in which these cases were found does not conform to a standardized population.

Table 2 shows the distribution of the group at the time of diagnosis by sex, age, roentgenographic classification, and disposition. Slightly over half of the employees continued at work after diagnosis and the remainder began to "cure."<sup>4</sup>

TABLE 3  
*Signs or Symptoms at Diagnosis*

SIGNS OR SYMPTOMS AT TIME OF DIAGNOSIS SINGLE OR IN COMBINATION	CHARACTER AND EXTENT OF LESION BY ROENTGENOGRAM*					
	Inactive		Questionably Active		Active	
	Number	Per cent	Number	Per cent	Number	Per cent
Total	204	100 0	301	100 0	87	100 0
No signs or symptoms	149	73 0	183	60 8	18	20 7
Fatigue	17	8 3	44	14 6	25	28 7
Cough	26	12 8	58	19 3	53	60 9
Hemoptysis	3	1 5	16	5 3	13	14 9
"Streaking"	4	2 0	4	1 3	6	6 9
Chest pain	11	5 4	42	14 0	18	20 7
Gastrointestinal symptoms	6	3 0	9	3 0	—	—
Pleurisy with effusion	—	—	4	1 3	2	2 3
Moist rales	1	0 5	11	3 7	22	25 3

\* See Table 6

In each classification a larger percentage of females than males began to "cure," and for both sexes a larger percentage began to "cure" at the younger ages than at the older ages.

Symptoms and physical signs at the time of diagnosis are shown in table 3. Among the males, signs and symptoms were more frequent at the younger ages, while among the females age does not seem to be an important factor. In the whole group about 60 per cent were asymptomatic. It is interesting to note that 20 7 per cent of the "active" cases and 60 8 per cent of the "questionably active" cases had no signs or symptoms. On the other hand, 3 5 per cent with lesions classified "inactive" had hemoptysis or "streaking," indicating the necessity for careful clinical study of all cases. Although fatigue and cough occur frequently among the tuberculous, it is not believed that their presence is necessarily of much

<sup>4</sup> "Cure" means cessation from work, treatment for tuberculosis, usually at the Company sanatorium at Mount McGregor.

importance in routine survey work. These complaints are encountered so frequently in nontuberculous employees that it is believed that their diagnostic significance is doubtful.

The incidence of overweight and underweight in the 592 was about the same as in our whole home office group.

Bilateral disease was found in 160 males and females but, since the experience of these persons proved to be similar to those in comparable groups whose lesions were unilateral but of the same extent, these cases are not differentiated in the tables.

As a fulfillment of the objective of the study, to discover an aid toward disposition and an indication of the future course and outcome, the recorded experience in relation to the "extent only" (minimal, moderately advanced, far advanced) of the disease at the time of detection was not particularly definitive. Performance was in general about what might have been expected. Those employees with advanced disease had a more serious health problem than those with minimal lesions. The advanced cases had more physical signs and symptoms, were advised more frequently to "cure," had a longer "cure" at the sanatorium, and had a higher mortality. "Extent" alone at the time of detection is not in itself of much help as an aid to disposition or medical recommendation.

But when the material is classified by a combination of *character* and *extent* of the disease, a more accurate prognosis can be made. It is true that some individuals in each group run a course contrary to the majority, but on an average the extent together with character of the lesion aid greatly in deciding the disposition of the case and indicate with surprising reliability the course and ultimate outcome. The length of "cure," the repetition of "cures," and the status on the first, fifth, tenth, and fifteenth anniversaries of diagnosis indicate markedly that the cases classified by roentgenogram as "inactive" had the lesser problem while the cases classified by roentgenogram as "active" had the most serious problem. The "questionably active" cases fell in between.

The length of cure at Mount McGregor was influenced by varying factors over the years. However, those with lesions classified as "inactive" "cured" the shortest time and none died, those with "questionably active" lesions "cured" longer and 2.9 per cent died, those with lesions classified as "active" had, on the average, the longest cures and 7.8 per cent died.

The experience in the first year of follow-up is depicted in figure 1. The definition of "satisfactory" means that the serial roentgenograms revealed stability or improvement of the lesion, significant signs or symptoms disappeared or were absent, and laboratory tests were negative. "Unsatisfactory" experience includes progression of the lesion as shown by serial roentgenograms, presence or development of significant signs or symptoms, or positive laboratory tests. Of those who began to "cure," about 80 per cent of the "inactive" cases had a satisfactory experience compared with a little over 50 per cent of the "questionably active" and about 25 per cent of the "active." Of those who continued at work, only 7.2 per cent of the "inactive" cases began to "cure" within a year compared with 33.3 per cent of the "questionably active" and 70.0 per cent of the "active." These were included in the group having "unsatisfactory" experience.

Of the 592 cases, 505 have been followed for five years or more, 377 for ten years or more, and 190 for fifteen years or more. Their status on their fifth, tenth, and fifteenth anniversaries of diagnosis and their interval history, divided by the character and extent of the lesion at the time of diagnosis, are shown in table 4.

It is interesting to note after fifteen years of follow-up that in the "inactive" group only 18.8 per cent had "cured" once, 10.9 per cent had relapses and none had died of tuberculosis. In contrast, in the "questionably active" group 45 per

Character of lesion by x-ray	SATISFACTORY	UNSATISFACTORY
<b>INACTIVE (169)</b>	84.6 %	82/12 <input checked="" type="checkbox"/> Started to cure during the first year
<b>? ACTIVE (129)</b>	53.3 %	12/4 33.3 %
<b>ACTIVE (10)</b>	2/0	0/0 70.0 %

#### BEGAN TO CURE AT TIME OF DIAGNOSIS

Character of lesion by x-ray	SATISFACTORY	UNSATISFACTORY
<b>INACTIVE (35)</b>	82.9 %	1/1
<b>? ACTIVE (172)</b>	54.7 %	45.3 %
<b>ACTIVE (177)</b>	26.0 %	74.0 %

FIG. 1. Experience in first year of follow-up. Continued at work at time of diagnosis under medical supervision.

cent "cured" once, 18.7 per cent had relapses in fifteen years, and 7.7 per cent died of tuberculosis, and in the "active" group all "cured" and 17.1 per cent had died of tuberculosis. The percentage of multiple "cures" in the "active" group was only 14.3. This apparently low figure was influenced by some very long first "cures" and by the high percentage of deaths.

The experience of the "inactive" group was distinctly more favorable than that of the "questionably active" group, and that in turn was more favorable than that of the "active" group. On the fifth, tenth, and fifteenth anniversaries of diagnosis, about three-quarters of the "inactive" group had worked continuously as compared with one-quarter of the "questionably active" group, and only one per cent of the "active" group. In general the experience for the males

in each group and at each anniversary was better than for the females, and the experience for the older groups was better than for the younger groups for both sexes

However, the experience of persons over age 40 with "inactive" lesions calls for special comment. In the early years of the program of continual observation, persons over age 40 with apparently healed lesions were given a roentgenographic examination every three years. It was noticed, however, that it was not uncommon to find unstable lesions in this older group after years of stability. In those days it was more usual to look for active tuberculosis in the younger group

TABLE 4

*Status and Interval History at Fifth, Tenth, and Fifteenth Anniversaries of Diagnosis According to Character of Lesion by Roentgenogram at Diagnosis*

ANNIVERSARY	TOTAL		AT WORK						CURING				DECEASED (TUBERCU- LOSIS)	
			Has worked con- tinuously		Has cured once		Has cured twice or more		First cure		Subsequent cure			
	Num- ber	Per- cent	Num- ber	Per- cent	Num- ber	Per- cent	Num- ber	Per- cent	Num- ber	Per- cent	Num- ber	Per- cent	Num- ber	Per- cent
Character and Extent of Lesion by Roentgeno- gram at Diagnosis*														
5th Anniversary														
Inactive	171	100 0	124	72 5	37	21 7	5	2 9	1	0 6	4	2 3	—	—
Questionably active	255	100 0	62	24 3	143	56 0	7	2 8	22	8 6	14	5 5	7	2 8
Active	79	100 0	1	1 3	53	67 1	2	2 5	14	17 7	3	3 8	6	7 6
10th Anniversary														
Inactive	129	100 0	93	72 1	25	19 4	7	5 4	1	0 8	3	2 3	—	—
Questionably active	182	100 0	44	24 2	101	55 5	18	9 9	1	0 4	9	5 0	9	5 0
Active	66	100 0	1	1 5	49	74 3	2	3 0	2	3 0	3	4 6	9	13 6
15th Anniversary														
Inactive	64	100 0	45	70 3	12	18 8	5	7 8	—	—	2	3 1	—	—
Questionably active	91	100 0	26	28 6	41	45 0	16	17 6	—	—	1	1 1	7	7 7
Active	35	100 0	—	—	24	68 6	2	5 7	—	—	3	8 6	6	17 1

\* See Table 6

although the U. S. Census statistics indicated that the death rate was highest for males at the older ages and for females at the younger ages. Although the group is small (table 5), the experience indicates clearly that "inactive," or apparently arrested tuberculosis should not be "forgotten" among older people and the necessity for continued periodic re-examination of all persons with lesions characteristic of tuberculosis should be emphasized.

Besides the experience with the home office employees another objective check is available on the efficacy of this classification and disposition. Since 1930 a decision has been made on 746 chest roentgenograms submitted by applicants for life insurance. Those showing lesions were divided into two groups: roentgeno-

logically, "active" and "inactive" tuberculosis. Since the groups were comparable in age distribution, the same percentage of deaths might have been expected in each group except for the chest condition as disclosed by the roentgenographic examination. It was found, however, that in the group of 178 classified by roentgenogram as "active" cases, 10.7 per cent had died of tuberculosis within nine years compared to 0.4 per cent in the group of 568 classified as "inactive" cases. The number of deaths from tuberculosis expected among white males of the United States of comparable age (1931-1940) was 0.7 per cent. These results have been published in detail elsewhere (3, 4).

This opportunity with its wide scope and years of follow-up among employees and applicants for life insurance has revealed many aspects of the tuberculosis problem not seen generally by phthisiologists. After analyzing the results of this

TABLE 5  
*Trends of Serial Roentgenograms during Five-Year Periods*  
*Employees who had never cured for Tuberculosis*

SEX	AGE	TOTAL	LESION STABLE	LESION BECOMING CALCIFIED	LESION UNSTABLE OR PROGRESSIVE
Males					
	40 to 44	22	18	1	3
	45 to 49	42	32	4	6
	50 to 54	48	42	2	4
	55 to 59	36	35	—	1
	60 to 64	26	18	1	7
Females					
	40 to 44	16	15	1	—
	45 to 49	17	16	—	1
	50 to 54	15	15	—	—
	55 to 59	13	9	—	4

carefully planned long range follow-up it is believed that it is possible to adopt a practical program of classification and disposition based upon the original roentgenographic examination. A satisfactory tuberculosis detection and control program may be instituted with safety for the individual patient if he is followed up carefully and advantageously for the community which can plan to use available treatment facilities.

The roentgenographic classification and suggested medical recommendation is shown in table 6.

#### DISCUSSION

When a person with an abnormal chest roentgenogram is detected in a routine case-finding survey, a recommendation and disposition must be made. In the majority of instances, conclusive clinical and laboratory evidence will be lacking to assist in this step. In the writers' experience a technically satisfactory roentgenogram (in this report "roentgenogram" means a technically satisfac-



TABLE 6

*Röntgenographic Classification and Medical Recommendation*

CLASSIFICATION OF LESION BY ROENTGENOGRAM	ROENTGENOGRAPHIC APPEARANCE	RECOMMENDATION	MEDICAL ACTION
Inactive	Extent Any minimal or borderline moderately advanced (N T A ) Character Fine or coarse strands, small or large calcific densities, small opaque areas with borders clearly outlined May be localized or scattered	Continue at work	Careful supervision and pe- riodic roentgenographic examination throughout life
Questionably active	A Extent Extensive min- imal or any moder- ately advanced (N T A ) Character Areas have general character- istics described above but tending toward "softness" B Extent Any minimal or borderline moder- ately advanced (N T A ) Character Areas of cloudy mottling or homogeneous densi- ties, borders hazy or not clearly defined, no suggestion of cav- ity	Observation as soon as possi- ble, preferably in a sanatorium for about three months	1 Careful study including serial roentgenograms and repeated sputum examinations. 2 Instruction in treatment and control of tubercu- losis 3 Individual without evi- dence of active tubercu- losis may return to work under careful supervi- sion and periodic roent- genographic examina- tion throughout life 4 Individual with evi- dence of active tubercu- losis to complete "cure "
Active	A Extent Far advanced (N T A ) B Extent Moderately ad- vanced (N T A ) Character Character- istics as II B, total excavitation must be less than 1 cm C New lesion Any shadow regardless of extent or character developing subse- quent to a roentgeno- gram interpreted as "normal" or "aver- age "	Admit to hospital or sanatorium immediately	Treat as active tuber- culosis and as circum- stances indicate

tory 14 by 17 celluloid film), interpreted in accordance with the classification as described, can be used as a basis for preliminary disposition. Further study and observation will modify or confirm the accuracy of the original decision. But it should be emphasized that there are distinct limitations to the use of roentgenography as follows:

A tuberculous lesion may be present and not visible on the film

A cavity may be present but not visible

"Hard" lesions may contain areas of definite activity

A tuberculous lesion may have healed without visible scar

Small lesions may be overlooked even by experienced radiologists

Group behavior can be forecast accurately, but there will be individual exceptions

Judgment and experience in interpretation are variable at present among physicians

Nevertheless, it is believed that the roentgenogram offers the best single bit of evidence in evaluating a case.

The experience of the roentgenologically "active" and "inactive" groups emphasizes the different behaviors of the extremes. Inevitably there is a "questionably active" group of cases which have about an even chance of becoming frankly "active" or proving to be "inactive." Whether it is better to treat this intermediate group as active tuberculosis is an open question concerning which opinions vary. The writers believe that the proposed plan of a relatively short period of education and intensive study, during which a more accurate estimation of the best procedure to follow can be made, offers a satisfactory solution.

As a result of the observations and experience in the present study, the writers have one unshaken conviction and that is that all cases with lesions which may be of tuberculous origin should have medical observation and periodic roentgenographic examinations throughout life.

#### SUMMARY

1 A technically satisfactory roentgenogram of the chest made in a routine case-finding survey can be classified so as to make a reasonably accurate preliminary disposition and long-range prognosis.

2 All persons whose roentgenograms disclose pulmonary involvement which may be tuberculous in character should have medical supervision throughout life.

#### SUMARIO Y CONCLUSIONES

*Tuberculosis. Estudio de la Disposición y Observación Subsiguiente a Base de la Naturaleza y Extensión de la Lesión Observada en la Radiografía Inicial*

Una radiografía técnicamente satisfactoria del tórax, obtenida en una encuesta colectiva corriente en busca de casos, puede ser clasificada de modo que permita hacer con bastante exactitud una disposición preliminar del caso y un pronóstico a largo plazo.

Todas las personas cuyas radiografías revelen afección pulmonar que pueda ser de naturaleza tuberculosa deben continuar bajo vigilancia médica toda su vida.

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# MINIATURE CHEST ROENTGENOGRAMS IN SCHOOLS AND INDUSTRIES IN SAN ANTONIO, TEXAS

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## INTRODUCTION

As part of the tuberculosis program, the Tuberculosis Control Division of the San Antonio City Health Department started a roentgenographic survey in the schools and industries located in the city. At the time the survey was started, the photofluorographic unit promised by the Texas State Department of Health was not available. Major Herman S. Wigodsky, Director of Research at the AAF School of Aviation Medicine at Randolph Field, aware of the work of the City Health Department, offered a 35 mm. mobile photofluorographic unit to the Tuberculosis Division for the purpose of carrying on the survey. All of the equipment and personnel to operate this unit were kindly furnished by the Air University, School of Aviation Medicine under the command of Col. H. G. Armstrong, M. C.

The mobile unit was created as one of the many improvements by the USSTAF in England during World War II. Wayburn's study of the AAF personnel surveyed by this unit in England, from April to September 1945, is a very interesting one and brings up the importance of mass roentgenographic surveys. Of the 77,016 persons examined, only 0.36 per cent had evidence of reinfection tuberculosis (13). This low incidence was to be expected, since the author was dealing with a particular type of population which had been screened at the time of induction. Most of the suspected and definite cases of tuberculosis had been previously eliminated from the ranks. Considering the number of months in the service (varying from twelve to fifty-five months or more), the mental and physical stress of soldiers in combat, and the not always ideal living conditions brought about by the war, the prevalence of tuberculosis in this group remained very low. The low percentage found in this study indicates that by intensive case finding and other tuberculosis control measures it is possible to maintain a low morbidity rate even when people are living under strenuous conditions.

In September 1945, the unit was sent back to the United States to be stationed at Randolph Field. Operating the unit during this summer was a team of six Army men, including the medical officer in charge. The medical officer, besides controlling the work of the unit, interpreted the films in collaboration with the Chief of the Tuberculosis Control Division of the City Health Department.

Prior to the examination of the several interested groups, the Bexar County Tuberculosis Association and the City Health Department carried out a preparatory health education program in order to inform such groups of the need for, and the advantages of, a chest roentgenographic survey. The Tuberculosis

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Association distributed literature, posters, and showed motion pictures. Educational talks were given by the Chief of the Tuberculosis Control Division and the Tuberculosis Association Health Educator.

In San Antonio the population is composed of three different racial groups: Group A<sup>2</sup>, Group B<sup>3</sup>, and Group C<sup>4</sup>. This racial grouping will be observed throughout the discussions in this paper. It is important to maintain this classification because of the prevalence of tuberculosis existing in Group B in this area (6, 10). The underprivileged socio-economic conditions under which Group B lives in this part of the country probably has an important influence on the prevalence of tuberculosis. In Mexico, according to Yelton (14), the tuberculosis death rate per 100,000 population was 56 as compared to 47 in the United States, a not very significant difference.

The results in this survey are based primarily on roentgenographic interpretations, therefore, subject to change after a more accurate and detailed study of the cases detected. All individuals found to have any chest involvement were referred to their private physician or to the City Chest Clinic for further study, care, and follow-up.

#### RESULTS

For purposes of discussion, the results of the survey will be divided into two groups: Schools and Industries.

##### *Schools*

Table 1 gives a general and detailed picture of the findings among the students examined. The percentages given include all persons examined roentgenographically in the schools, that is, students, teachers, clerical staff, and other personnel, and also some parents and relatives in one of the schools. Eight thousand, nine hundred eighty-three persons were examined, of which 51.1 per cent belonged to Group A, 36.7 per cent to Group B, and 9.2 per cent to Group C. Eleven Chinese and one Japanese were included in this last group (table 1).

Of the 8,983 persons examined, 43, or 0.48 per cent, showed evidence of reinfection tuberculosis. By breaking down the total number of persons examined into racial groups, it is observed that of the 4,864 of Group A examined, 14, or 0.29 per cent, showed evidence of reinfection tuberculosis, of the 3,291 of Group B examined, 27, or 0.82 per cent, had evidence of reinfection tuberculosis, and, finally, of the 828 of Group C examined, 2, or 0.24 per cent, had roentgenographic evidence of reinfection type tuberculosis.

It is of interest to observe that Group B showed a higher percentage of tuberculosis than Group A. The low percentage among Group C may be attributed to the small number examined roentgenographically and also to their much better standard of living in this part of the country, while the opposite is true of Group B. These facts may distort the true picture of tuberculosis prevalence among

<sup>2</sup> White, excluding Mexican Nationals and those of Mexican descent.

<sup>3</sup> White Mexican Nationals and those of Mexican descent.

<sup>4</sup> Negro.

TABLE 1  
Schools

Number of Persons Examined and Number and Percent with Reinfection Tuberculosis by Race, Sex and Age, San Antonio, Texas, 1947

AGE	RACE																				
	Group A				Group B				Group C												
	Sex																				
	Males		Females		Males		Females		Males		Females										
	Number/ examined TB	Per cent	Number/ examined TB	Per cent	Number/ examined TB	Per cent	Number/ examined TB	Per cent	Number/ examined TB	Per cent	Number/ examined TB	Per cent									
0 to 4	0		2		0		0		0		0										
5 to 9	17		13		0		10		0		0										
10 to 14	455		434		15		208		0		0										
15 to 19	1,749		1,006		244		1,290		46		0										
20 to 24	6	34	2	12	5	41	15	116	213*	1	41	2934									
25 to 29	116		64		73		22		644		0	10									
30 to 39	29		37		13		17		49		0	6									
40 to 49	25		99		4		28		28		0	17									
50 to 59	33		94		6		20		9		0	6									
60 and over	11	30	0		5		6		2		0	4									
Unknown	8	18.2	0		3		5		0		0	0									
	3		20		5		5		1		0	3									
Total	2,416	9	2,418	5	21	1,500	7	41	1,701	20	118	142	1	23	386	1	26	8,983	43	48	
Total reinfection TB																					

\* 4 Chinese, 1 Japanese

† 3 Chinese

‡ 1 Chinese

them According to Picnot, the annual family income most prevalent among Group B was \$622.34, Group C, \$937.50, and Group A, \$949.02 The most prevalent individual incomes of these three respective groups were Group B, \$141.44, Group A, \$256.49 and Group C, \$284.09 (7)

Comparing the percentages found by race and sex, the only striking difference is observed among the females in Group B where 1.18 per cent had roentgenographic findings of reinfection tuberculosis Similar findings are observed in the age group 15 to 19 where 1.16 per cent showed evidence of tuberculosis, while for the other racial groups and sexes the percentages remained under one

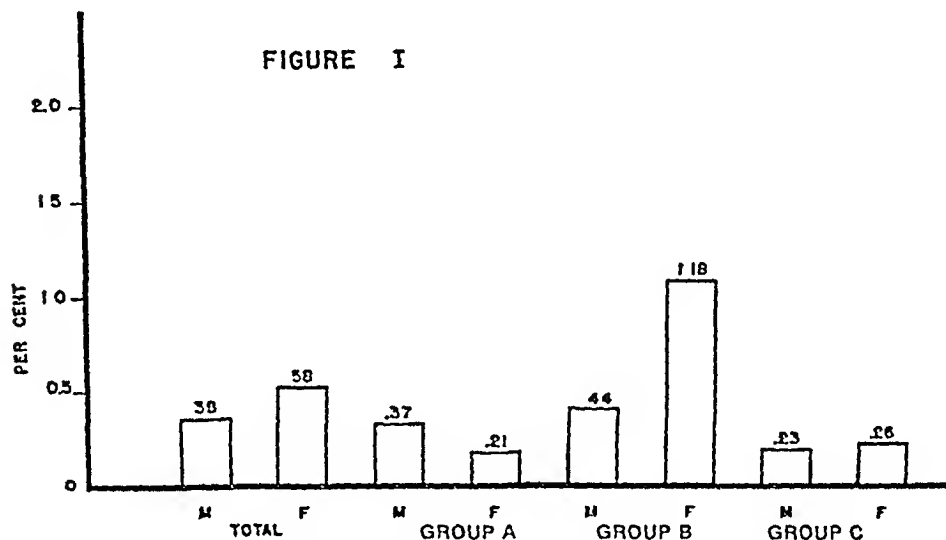


FIG. 1 Per cent reinfection tuberculosis among students, by race and sex, in San Antonio, Texas, 1917

It is of interest to break down table 1 and obtain the percentages in the age groups 10 to 21, which include most of the high school and college students. Another reason for choosing this age group is that in San Antonio tuberculosis prevails in the age group 10 to 39, as can be seen in the following chart (figure 2)

In table 2 it is seen that among the total of Group A (1,121) examined in age group 10 to 21, 11, or 0.25 per cent, had evidence of reinfection tuberculosis, of the 3,117 of Group B, 22, or 0.76 per cent, had evidence of the disease, and, finally, of the 703 of Group C, 2, or 0.28 per cent, showed evidence of reinfection tuberculosis. Of the total number of persons examined in this age group (8,271), 37, or 0.45 per cent, showed evidence of tuberculosis. As can be observed, the total percentages differed slightly, 0.48 per cent for the total group examined and 0.45 per cent for the age group 10 to 21. Differences are more noticeable when taking the racial groups individually, either as a total or by the age group in question, in either of which Group B reveals a higher percent than the other two groups examined.

In spite of the limited number of roentgenograms taken among the schools in San Antonio and Bexar County, these findings are very similar to those observed in other states. Edwards in New York found the percentage of clinically

**FIGURE 2**  
**DEATHS**

	1 ST	2 ND	3 RD	4 TH	5TH & 6TH	
1-4				4		1926-30
5-9		12				
10-19	34					
20-29	34					
30-39	21					
40-49		13				
50-59				8		
60-					4	1941-45
	1 ST	2 ND	3 RD	4 TH	5TH & 6TH	
1-4			13			
5-9			11			
10-19	33					
20-29	41					
30-39	24					
40-49			11			
50-59			7			
60-					4	

FIG 2 Per cent and rank of tuberculosis as a cause of death in two selected five year periods of time, in San Antonio, Texas, 1926-1930 and 1941-1945

significant tuberculosis to be 0.2 in 16,000 college students (8). According to a publication of the United States Public Health Service (12), school surveys conducted in various states showed only slight fluctuation in the results. In Michigan, for example, 2,788 students were examined roentgenographically and 0.3 per cent were found to have reinfection tuberculosis. In Alabama, 7,770 students were examined and showed evidence (0.4 per cent) of tuberculosis. Similar studies





in Florida (13,000 students), New York (16,128), and District of Columbia (3,084) showed percentages between 0.5 and 0.7 per cent. In contrast, in San Antonio and Bexar County, 0.48 per cent of students with reinfection type tuberculosis were found among 8,983 examined. Considering all states surveyed, 81,529 chest roentgenograms were made and of these 452 had evidence of reinfection pulmonary tuberculosis, thus giving a percentage of 0.6 per cent. In

FIGURE 3

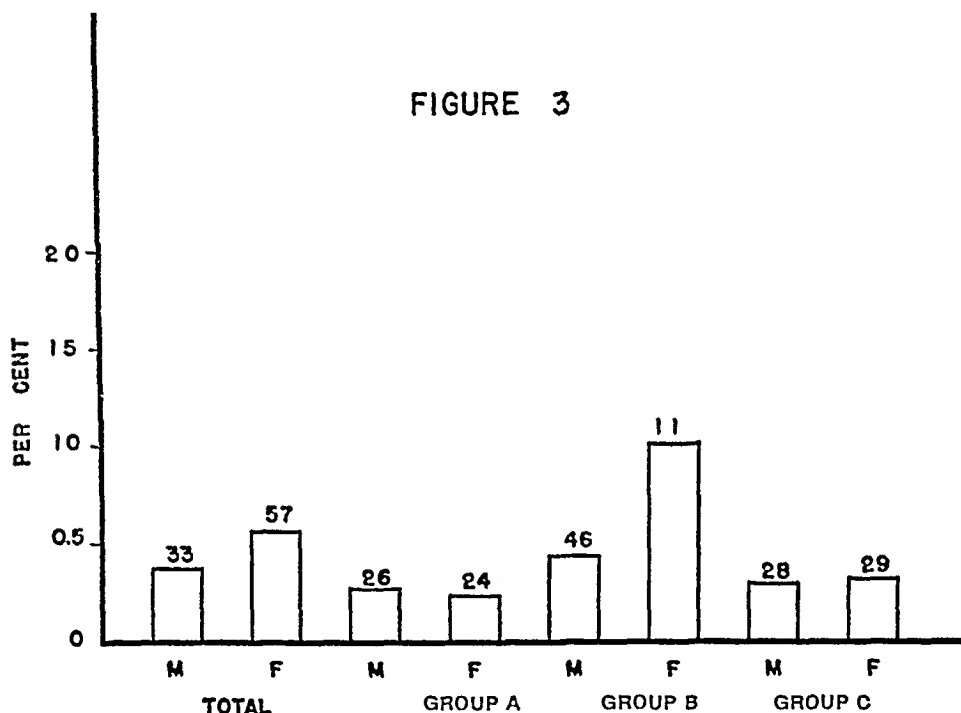


FIG 3 Per cent reinfection tuberculosis among students in age group 10 to 24 by race and sex in San Antonio, Texas, 1947

TABLE 3

*Nontuberculous Pathology among Students Examined in San Antonio, Texas, in 1947*

Bone disease	13	Diagnosis reserved	3
Cardiovascular	6	Bronchiectasis	2
Pleural abnormalities	4	Tumor masses	1

the Public Health Service study, as well as in the present one, the same class of persons was included, that is, students, teachers, and maintenance personnel of high schools and colleges.

An interesting survey was made by R. Tak Eng in Hong Kong, China, in 1940-1941, prior to Japanese occupation. Eng reports that 4,614 students were fluoroscoped and that 124, or 2.3 per cent, had pulmonary tuberculosis. This

incidence is very high, but, as remarked by the author, "the population of Hong Kong had increased to three times its normal in the three years preceding our survey. Refugees had flocked in from various parts of China, making proper housing, nutrition and sanitation difficult" (2). Again, the importance and influence of the socio-economic status stands out in the picture of tuberculosis prevalence.

Of incidental interest is the presence of chest disease other than tuberculosis, which was found in 0.32 per cent of the total persons examined. The predominating age group for nontuberculous pathology was 15 to 19, with 21 of the 29 persons found falling into this group.

### *Industries*

In the eighteen industrial groups examined, workers for the Community Chest service and from one of the insurance companies of San Antonio were included, also 266 ranchers and stockyard employees not directly associated with industry. The remaining groups were employed by industrial plants in the city. The total number of the nonindustrial workers examined roentgenographically was not large enough to influence the findings, they were, therefore, kept in the total group.

The high percentage of tuberculosis found in industry has caused a debate among all authors studying roentgenographic surveys of industrial workers. Is it true that the prevalence of tuberculosis is higher among industrial workers or should the known fact that a higher incidence exists among unskilled workers be taken into consideration? Goldberg says "The death rate among the unskilled worker is more than twice that of the skilled worker." He continues, "Limited earning capacity has a direct relationship to tuberculosis in industry" (3).

A more thorough investigation should be made to ascertain the true value of these findings among industrial workers. The importance of the socio-economic status of the groups examined must always be borne in mind because this will definitely influence the prevalence of the disease. This fact cannot be overlooked in San Antonio where 40 per cent of the total population falls within Group B with very limited earning capacity (6, 10).

Martin, Pessar, and Goldberg (3) found 2.3 per cent of clinical tuberculosis among food-handlers. In San Antonio, in a study of 17,700 food handlers examined roentgenographically at the City Health Department, a percentage of 3.3 was found, of which 1.8 per cent were suspects and 1.5 per cent definite (6). Merriweather, Savers, and Lanza (3) reported 2.1 per cent and 2.6 per cent, respectively, for the years 1928 and 1929 in lead and zinc miners of Oklahoma, Kansas, and Missouri. The presence of silicosis may be responsible for the high percentage, since diagnosis was established by roentgenographic findings alone. A report of the U. S. Public Health Service of surveys in industry for the years 1912 to 1916 revealed a percentage of 1.1 for this country (11). Hilleboe, reporting on roentgenograms taken among industrial workers throughout the country, in 1912 to 1914 gives the figure 1.5 per cent for the prevalence of pulmonary



FIGURE 4

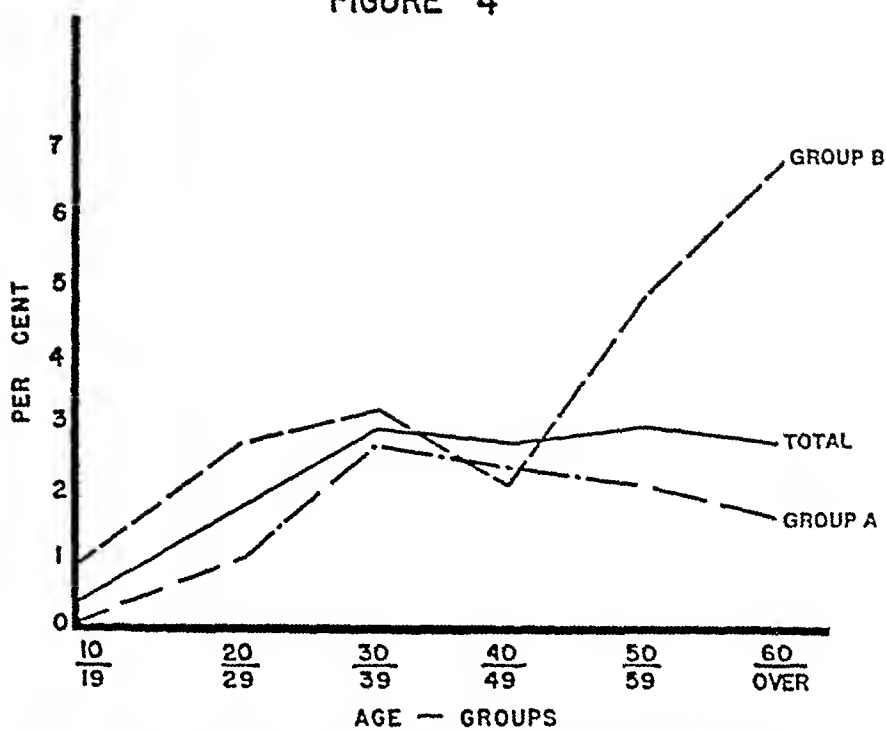


FIG 4 Comparative percentage curves of reinfection tuberculosis (exclusive of local Negroes) among industrial workers, by race and age, San Antonio, Texas

FIGURE 5

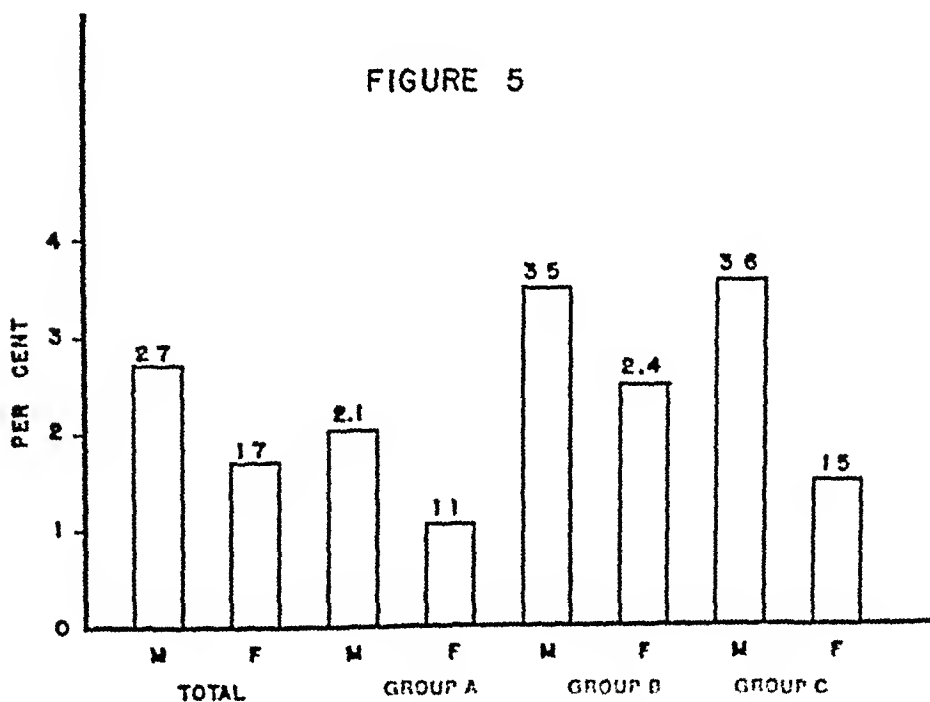


FIG 5 Per cent reinfection tuberculosis among industrial workers, by race and sex, in San Antonio, Texas, 1917

tuberculosis among these adults (5) Elkin, Irwin, and Kurtzhalz in Philadelphia in 1942 examined 71,767 industrial workers and found 2.3 per cent with evidence of reinfection tuberculosis, based solely on the interpretation of the survey films (1) The same figure, 2.3 per cent reinfection tuberculosis, was observed in this survey made in San Antonio in which 3,132 roentgenograms were obtained and 73 persons had reinfection type tuberculosis. The findings by age groups, race, and sex are presented in table 4.

Fifty-three per cent of the total individuals examined were in Group A, 40.4 per cent belonged to Group B, and 6.6 per cent to Group C. This percentage distribution is similar to the one observed among the schools and also to the city's population percentage distribution which is composed of 53 per cent in Group A, 40 per cent in Group B, and 7 per cent in Group C (6). Since the same percentage distribution holds true in the industrial sample as it does in the city's population, this sample should give a fairly accurate picture of the prevalence of tuberculosis in the San Antonio industrial groups examined.

Of the 3,132 persons examined, 73, or 2.3 per cent, had roentgenographic evidence of reinfection tuberculosis. Dividing the total number examined into racial groups, 1,660 in Group A were examined, of whom 29, or 1.7 per cent,

TABLE 5

*Nontuberculous Pathology Among Industrial Workers Examined in San Antonio, Texas, in 1947*

Cardiovascular	10	Pneumoconiosis	3
Bone disease	5	Tumor masses	2
Pleural abnormalities	4	Diagnosis reserved	2
Bronchiectasis	3	Fibrosis	1

showed evidence of the disease, of the 1,264 in Group B examined, 39, or 3.1 per cent, had findings of tuberculosis, and of the 208 in Group C, 5, or 2.4 per cent, had roentgenographic evidence of tuberculosis of the reinfection type.

The total reinfection tuberculosis percentage curve rose from 0.5 per cent in the age group 10 to 19 to 3.1 per cent in the age group 50 to 59. This percentage curve rises progressively to a peak in the older age groups, as is observed in the usual tuberculosis morbidity curves. Of importance was the difference in the racial groups, where those in Group B have a curve which stands higher throughout the different age groups with a drop in the 40 to 49 age groups and a second rise in the age groups 50 and over. This may be seen in figure 4.

The findings for those in Group C have not been placed in figure 4 because only two age groups were represented with very high incidence, causing a false representation of the prevalence of tuberculosis among them.

Also of interest were the 30 cases (0.95 per cent) of nontuberculous disease of the chest found among the 3,132 persons examined. Examining these 30 cases by age, it is observed that the majority of the cases is in the age groups above 40 with the highest number in the age group 50 to 59. These persons were referred to their private physicians and to the city chest clinic for further investigation and follow-up.

## SUMMARY

The roentgenographic findings in a chest survey of 12,115 students and industrial workers in the city of San Antonio, Texas, are as follows:

A total of 8,982 students were examined and 43, or 0.4 per cent, showed evidence of reinfection tuberculosis. Of the total, 4,864 were in Group A<sup>1</sup>, of whom 14, or 0.29 per cent, showed roentgenographic evidence of tuberculosis, 3,291 were in Group B<sup>1</sup>, with 27, or 0.82 per cent, having pulmonary reinfection type tuberculosis, and 828 were in Group C<sup>1</sup>, of whom 2, or 0.24 per cent, had roentgenographic evidence of the disease.

A total of 3,132 industrial workers were examined and 73, or 2.3 per cent, had evidence of reinfection tuberculosis. Of the total, 1,660 were in Group A, of whom 29, or 1.7 per cent, had evidence of pulmonary tuberculosis, 1,264 were in Group B with 39, or 3.1 per cent, with evidence of reinfection tuberculosis, and 208 were in Group C, of whom 5, or 1.5 per cent, showed evidence of reinfection pulmonary tuberculosis.

In this study the prevalence of tuberculosis among those in Group B is higher throughout all age groups, either in the schools or the industrial workers examined.

Emphasis was placed on the socio-economic status of those in Group B and its relationship to the prevalence of tuberculosis among them in this part of the country.

In this survey, other abnormalities of the chest were found in 0.32 per cent of the students, with bone involvement as the primary finding. Of the industrial workers examined roentgenographically, cardiovascular abnormalities prevailed among the 0.95 per cent of the nontuberculous chest findings.

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# Case Reports

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## MILIARY TUBERCULOSIS CAUSED BY INTRAVENOUS SELF-INJECTION OF TUBERCLE BACILLI, TREATED SUCCESSFULLY WITH STREPTOMYCIN THERAPY<sup>1</sup>

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(Received for publication May 27, 1949)

A case of miliary tuberculosis caused by the intravenous injection of a massive dose of virulent tubercle bacilli gives the clinician a rare opportunity to study this disease under ideal circumstances for investigation. The following is a case study of a 30-year-old unmarried female, an experienced bacteriologist, who injected herself intravenously with 10 cc of suspension of virulent strain of tubercle bacilli with possible suicidal intent. The injection was made into the left antecubital vein. She stated that she prepared the inoculum by washing a few cc of saline over a slant of Petraghani's medium which contained a 14-day growth of *M. tuberculosis*. The culture represented a primary isolation from the pleural fluid of a young man with an acute tuberculous pleurisy. An interesting background to this episode is the fact that three years previously, while inoculating a guinea pig, she had accidentally punctured the skin of her left antecubital fossa with a needle contaminated with tubercle bacilli. Following this, she noticed a very small superficial papule at the puncture site which disappeared after a few weeks and was not associated with further swelling, induration, tenderness, or any systemic symptoms. Previous to this episode in 1945, she does not remember having had a tuberculin skin test. One year after the 1945 incident, however, a tuberculin skin test was positive.

The patient (L F) was admitted to St. Luke's Hospital on January 15, 1948, the day following the intravenous injection, but did not reveal any information concerning her self-inoculation. Instead, she complained of a five pound weight loss, night sweats, fatigue, urinary frequency, "pus in her urine," and a chronic nonproductive cough of three months duration. She emphasized the fact that she had worked in a Veterans Hospital for tuberculosis in 1945.

The patient was referred to the urology service with a tentative diagnosis of pyelonephritis, possibly tuberculous in origin. Her temperature at the time of admission was 101.8° F, which subsided to normal on her second hospital day. The patient later stated that her temperature had gone to 104°F a few hours after the injection and was on the way down (101.8°F) when she was admitted to the hospital. She remained in the hospital for eight days during which she continued to be afebrile and asymptomatic except for the first day. Her blood count, routine urine examinations, urea nitrogen, and erythrocyte sedimentation rate were all within normal limits. A chest roentgenogram showed no abnormal densities in her lungs. Cystoscopy revealed the findings of a subsiding infection in the bladder. Pyelography showed pyelectasis and some clubbing of the calyces of the left kidney. Cultures (Petraghani's medium) of the urine of the bladder and both ureters, however, revealed no tubercle bacilli. A guinea pig inoculated with a twenty-four hour urine specimen taken at this time revealed no evidence of tuberculosis on subsequent examination.

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At the time of this admission, there was no mention of a lesion in the left antecubital fossa, but the patient later stated that on the day following her injection she had noticed swelling, redness, and tenderness at the injection site. She had squeezed a small amount of serum from the lesion and had seen tubercle bacilli in a smear of this material.

After eight days of study the patient was discharged. On the following day, nine days after the injection, she again began to have severe chills and fever. She was readmitted on the fifteenth day after the injection with a temperature of 101°F. At this time she admitted for the first time that she had injected herself with tubercle bacilli. Considerable skepticism met this confession, however, and therapy was delayed for six days until a more positive diagnosis could be made. Physical examination was essentially negative except for a small, one mm. raised, slightly tender area in the left antecubital fossa (figure 1). There was no enlargement of the left epitrochlear or axillary lymph nodes. The total erythrocyte and leukocyte counts and examinations of the urine revealed no abnormalities. Serum agglutination reactions for typhoid, paratyphoid, brucellosis, and typhus were negative and no malarial parasites were seen on examination of the blood. The erythrocyte sedimentation rate was 56 mm. in one hour.

A chest roentgenogram obtained January 31, 1948 (figure 2) revealed no abnormalities after six days of a bounding fever with daily spikes up to 104°F. Streptomycin therapy



FIG. 1. Tuberculous lesion at the site of vaccination in left arm.

(30 Gm. daily by the intramuscular route) was instituted because of the appearance of a generalized milary infiltration throughout both lungs, as shown in chest films taken February 4, 1948 (figure 3). The infiltration had appeared at some time between the sixteenth and twenty-first days after the inoculation with tubercle bacilli. At this time (February 4) large numbers of acid fast bacilli were seen on examination of a smear prepared from a small amount of serum expressed from the lesion in the left antecubital fossa. Cultures (Dubos, Petri goni) of this material were subsequently positive for *M. tuberculosis*. A tuberculin skin test with 1:100,000 dilution O.T., performed on February 5, was negative after forty-eight hours' observation.

Repeated blood cultures on both Petri goni and Dubos medium obtained after the start of streptomycin therapy were sterile. Moreover, subsequent guinea pig inoculation of the patient's blood, urine, and cerebrospinal fluid yielded negative results. The cerebrospinal fluid sugar, protein, chlorides, gold curve, and microscopic examination remained normal throughout the patient's hospital stay. Frequent microscopic examinations of the urine over a period of three months showed no abnormalities. The total leukocyte and differential counts remained within normal limits, whereas the patient showed a mild hypochromic, microcytic anemia one month after the beginning of her illness. This was subsequently corrected with the help of one 500 cc. whole blood transfusion, the administration of iron sulfate, and control of her infection.

The only areas manifestly affected by this massive injection of tubercle bacilli were the site of the injection and the lungs. The tip of the spleen was barely palpable on one occasion eight days after admission to the hospital during the height of the fever. Subsequent examinations, however, revealed no consistently demonstrable splenic enlargement. The ocular fundi showed no abnormalities at any time. Sputum examinations for tubercle bacilli were

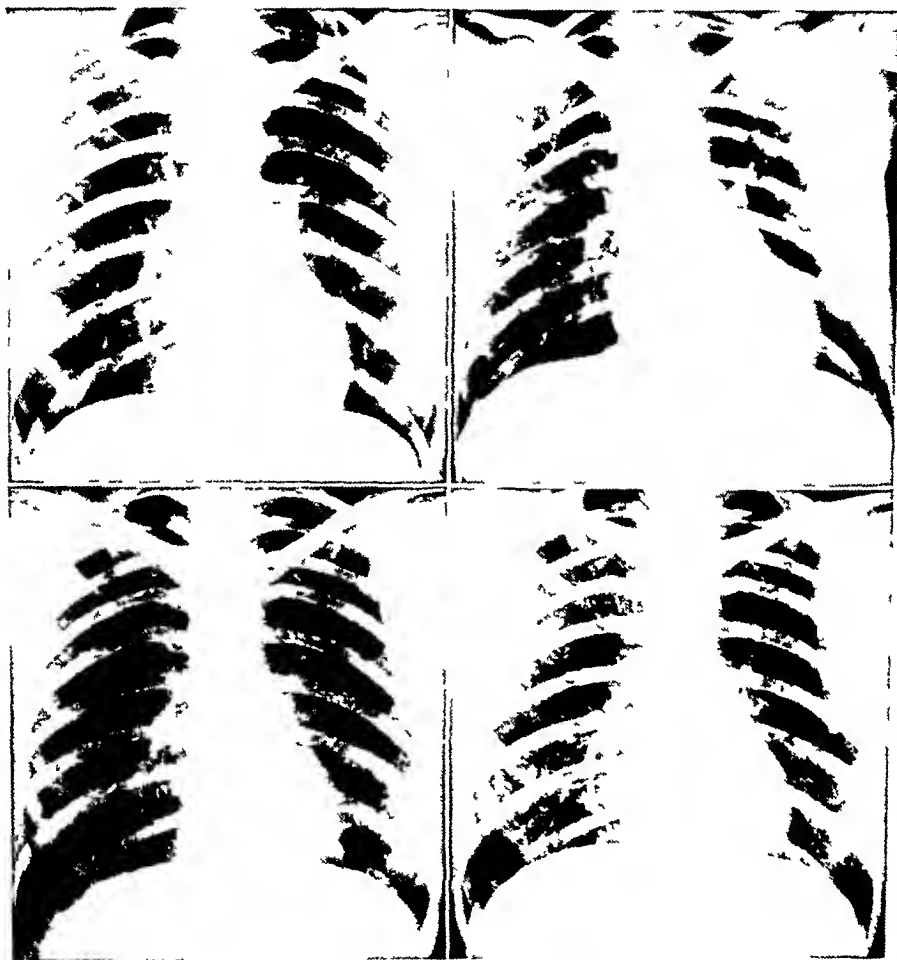


FIG. 2 (Upper left) Chest roentgenogram (January 31, 1948) obtained sixteen days after infection. No abnormalities are present.

FIG. 3 (Upper right) Chest roentgenogram (February 4, 1948) revealing miliary dissemination 20 days after infection.

FIG. 4 (Lower left) Chest roentgenogram (February 19, 1948). Miliary lesions are still well defined 36 days after infection.

FIG. 5 (Lower right) Chest roentgenogram (March 6, 1948). Miliary lesions seem to be more sharply outlined 51 days after infection.

negative on two occasions. A tuberculin skin test, 1:10,000, was positive after forty-eight hours on the twenty-sixth day after the inoculation. No significance was attached to this positive reaction because of the history of a previously positive tuberculin skin test in 1946.

It is probable that the immunity provided by the infection prior to 1946 was minimal.

in the presence of so great a dose of injected tubercle bacilli. The lungs had apparently filtered out the majority of injected bacteria, thus preventing, with the help of streptomycin therapy, hematogenous spread to the other organs of the body.

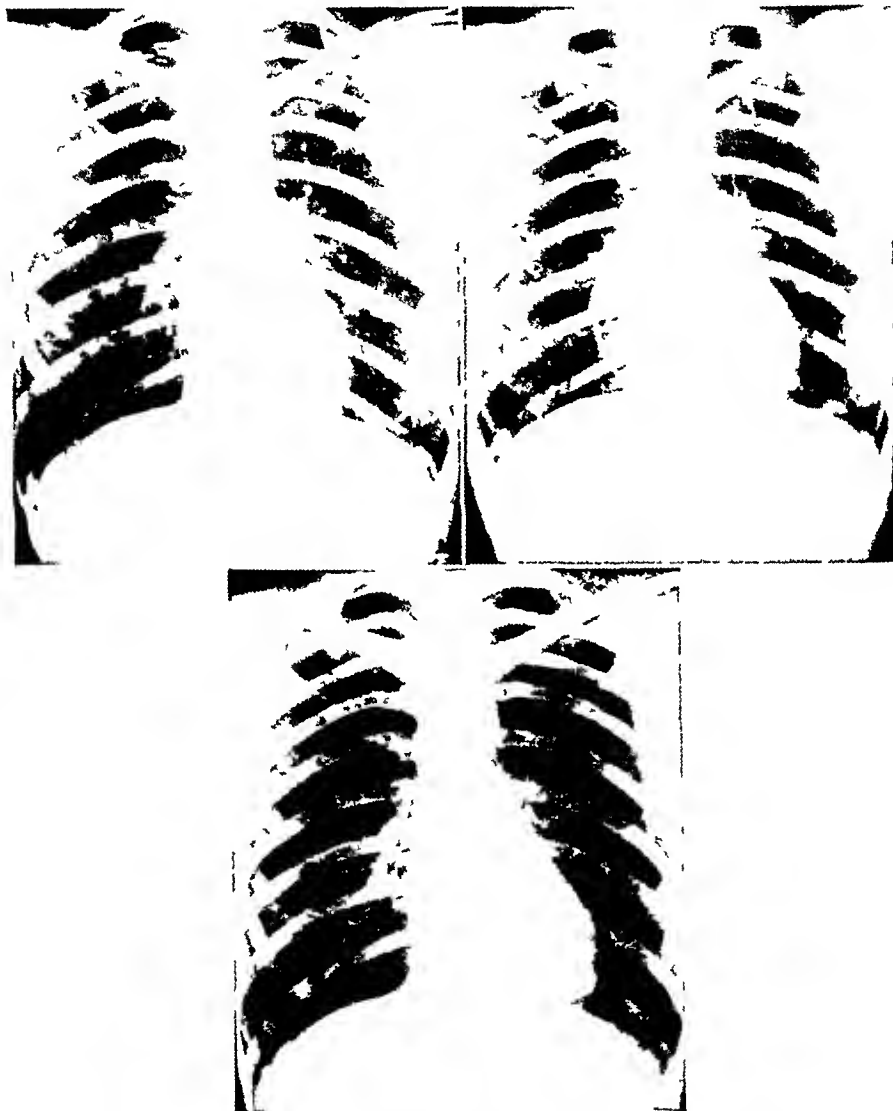


FIG. 6 (Upper left) Chest roentgenogram (April 8, 1948). Miliary lesions are now beginning to fade, 72 days after infection and after 53 days of streptomycin therapy.

FIG. 7 (Upper right) Chest roentgenogram (May 7, 1948). Lesions in lungs still resolving.

FIG. 8 (Lower) Chest roentgenogram (July 26, 1948) reveals no abnormalities.

There were available as indices of the success of streptomycin therapy the chest roentgenograms, determinations of the erythrocyte sedimentation rate and temperature readings, the local abscess at the site of injection, and the patient's subjective improvement. She remained on the original dose of streptomycin (3.0 Gm. daily) for nineteen days with

little or no definite improvement in the symptoms of general malaise, headaches, and shaking chills. Her temperature remained elevated with daily spikes to 103° to 104°F. During this time (February 19) a chest roentgenogram showed that the pulmonary lesions in the lungs were more sharply circumscribed and increased in number (figure 4). The lesion in her left antecubital fossa had not improved since the initiation of therapy. In the belief that larger doses of streptomycin might control the infection, the dose was increased to 5.0 Gm. a day and continued for four days without apparent improvement. The dose was then reduced to 2.0 Gm. of streptomycin per day because of the lack of improvement and severe vertigo.

At this time (February 23) the patient began to complain of a rather severe pain in the area of the venipuncture. Wet dressings were applied to the site of the injection and these seemed to give relief. On the following day, the puncture wound opened and considerable thick, yellowish pus was discharged. Following this, the patient's temperature dropped to 100°F and remained there for seven days and then fell to 99°F.

From the twenty-third day of therapy, the patient's feeling of well-being improved dramatically. A roentgenogram of the chest taken on the thirty-eighth day of therapy (March 6, 1948) showed the lesions in the lungs to be static (figure 5) and the lesion on the left arm was definitely improved.

From the thirtieth day of therapy, the patient's temperature remained normal and a chest roentgenogram on the sixty-fifth day of treatment showed definite improvement in the lung lesions (figure 6). At this time (April 8, 1948) the lesion on the left arm had completely healed, and the patient had no symptoms except for moderate dizziness from the streptomycin therapy. No auditory changes were observed in serial audiograms.

One of the most fortunate factors aiding the recovery of this patient was the fact that the tubercle bacilli initially cultured from the lesion in the left antecubital fossa (Dubos medium) showed sensitivity to a concentration of less than 1.0  $\gamma$  of streptomycin per cc.

The patient received a total of 241.0 Gm. of streptomycin over a period of 105 days. She was discharged to her home on her one hundred and twenty-fifth hospital day with no recurrence of symptoms following cessation of therapy. Her last roentgenogram obtained three weeks before discharge (figure 7, May 7, 1948) showed the lesions in the lungs to be less intense and more sharply circumscribed than on previous examinations. The erythrocyte sedimentation rate at the time of discharge was 21 mm. in one hour.

This patient has been carefully followed and a report from her physician in July 1948 stated that she was exercising moderately, felt well, and had gained weight. A chest film, July 26, 1948, revealed no abnormalities whatsoever (figure 8).

A letter received in October from this very fortunate young lady stated she had been working since September in a blood bank in the hospital of her home town. She also stated that her health was fine and confirmed this statement by the news of her marriage in early September 1948.

#### DISCUSSION

A review of the literature has revealed only one other case similar to the one presented here. The case of Lemierre and Ameuée was that of a twenty-nine year old male who injected himself with a large dose of tubercle bacilli intravenously and developed pulmonary tuberculosis, shown in serial roentgenograms of his lungs, between the ninth and thirty-sixth day after injection. In this case streptomycin was not available, and the patient died at the end of three months. There were several significant differences between these two cases.

1. The French patient, without the aid of streptomycin, became progressively worse and roentgenographic examinations revealed increased size and distribution of the pulmonary lesions. Twelve days before death, the pulmonary lesions became confluent and caused marked respiratory embarrassment. Moreover, splenic enlargement persisted and the patient developed tuberculous meningitis eight days before death.

2 In contrast, in the present case the lung had apparently filtered out the tubercle bacilli, preventing further hematogenous spread

3 The French patient did not develop anemia in spite of severe wasting and malnutrition

4 Our patient showed normal leukocyte and differential counts throughout her illness. The French patient demonstrated a leukopenia, 2,600, and a mononucleosis at the beginning of his illness. This gradually reverted to normal and then to a leukocytosis of 12,500 with 90 per cent polymorphonuclear leukocytes in the terminal stage of his disease

5 Our patient developed an initial fever immediately after the injection lasting forty-eight hours, and then her temperature remained normal for nine days before rising to 101°F. The French patient developed a fever within forty-eight hours which persisted until death three months later

The similarities between the two cases were

1 The mode of injection was intravenous in both cases

2 The latent period from the time of injection to the appearance of pulmonary lesions was between sixteen and twenty-one days in our case, and between nine and thirty-six days in the French patient

3 Both patients had a positive tuberculin skin test prior to the injection of tubercle bacilli

4 In neither case was it possible to obtain tubercle bacilli on cultures of the blood on Petriagarum and Dubos media in our case and Loewenstein's medium in the French case

It is believed that everyone will agree that this case presents one of the most interesting experiments in the pathogenesis and treatment of hematogenous tuberculosis in the human ever to be recorded. A careful attempt was made to note all of the pertinent facts which could be observed and determined through the study of this patient

At the outset of the infection, it was suggested that the original site of the puncture should be totally excised but it was decided not to do this. It now appears that the procedure might have been beneficial, as the subsequent course of the patient showed very clearly that the streptomycin therapy had no effect on the infection until the original feeding focus sloughed out. The fall in temperature and the loss of symptoms coincided very definitely with the evacuation of the original abscess

The possibility exists that certain cases of miliary tuberculosis might be saved by the combination of streptomycin therapy and the eradication through surgery of the area in the body from which the tubercle bacilli are disseminating

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# ABDOMINAL PNEUMOCELE FOLLOWING ARTIFICIAL PNEUMOPERITONEUM<sup>1</sup>

H C WORTMAN<sup>2</sup> AND H E BASS

(Received for publication March 4, 1949)

Artificial pneumoperitoneum has become an accepted treatment for pulmonary tuberculosis. Recent months have seen an increasing number of reports regarding the results of this form of therapy (1-4). A comprehensive monograph has also been devoted to the subject (5). Aside from the latter work, little if any mention has been made of the roentgen appearance of air-containing circular shadows or pneumoceles in the abdominal cavity following artificial pneumoperitoneum. The following case reports are presented to illustrate the roentgenographic features of this condition.

## CASE REPORTS

*Case 1* The patient was a 24 year-old white male who developed cough and dyspnea in December 1945. He was admitted to a general hospital in March 1946. The sputum was positive for tubercle bacilli and roentgenographic examination showed evidence of left upper and lower lobe cavitation with a right upper lobe infiltrate. A right pneumothorax was attempted in June 1946 but was unsuccessful. A left phrenic crush was performed in December 1946. In May 1947, a left pneumothorax was unsuccessful in closing the left upper lobe cavity. He was admitted to Halloran Veterans Administration Hospital in June 1947 and the left pneumothorax was continued until March 1948, when it was abandoned. On March 7, 1948 a pneumoperitoneum was initiated with good elevation of the diaphragm. In July 1948, the patient's sputum became negative for tubercle bacilli and has continued negative to the present time. Since September 1948, the cavities previously seen are no longer visible on chest roentgenograms.

Shortly after the initiation of the pneumoperitoneum, a pneumocele was demonstrated on the right side, just above the upper surface of the liver (figure 1). Subsequently, the intra-abdominal pressures were increased for therapeutic reasons by means of increased refills given at more frequent intervals. A film taken at this time (figure 2) showed increased ballooning of the pneumocele, which now extends almost to the lateral wall of the abdominal cavity. A film taken just before a refill during a period of decreased abdominal pressure showed some collapse of the air-containing shadow which exhibited an indented, serrated border (figure 3).

*Case 2* The patient was a 40 year old white male who on routine separation film in October 1945 was found to have an exudative infiltrate involving the entire right upper lobe with cavitation and spread of disease to the left second and third interspaces with multiple small cavities. The sputum was positive for tubercle bacilli.

A right pneumothorax was instituted at a general hospital in November 1945 but numerous adhesions prevented adequate collapse. A left pneumothorax was initiated in January 1946 but was abandoned as ineffective. In May 1946 following an unsuccessful attempt at pneumolysis, a right pleural effusion developed and the pneumothorax on the right side was also discontinued. The aspirated fluid was positive for acid fast bacilli and the patient began running a toxic course. In August 1946 he was started on a course of streptomycin.

<sup>1</sup> Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

<sup>2</sup> Resident physician, Tuberculosis Service, Halloran Veterans Administration Hospital, Staten Island, New York.

for 120 days with clinical improvement. In February 1947, there was a spread of disease in the left lung and streptomycin was again given for a 120-day period. Pneumoperitoneum was instituted with the hope that it would help control his disease so that thoracoplasty might be performed at a future date.

The patient was transferred to Hillier Veterans Administration Hospital in June 1947. The pneumoperitoneum was continued. He showed subjective improvement in spite of extensive bilateral disease with cavitation. In May 1948, the patient developed a spontaneous pneumothorax on the right side with a small amount of fluid. The pneumoperitoneum has been maintained.

A roentgenogram taken during the course of pneumoperitoneum therapy (figure 4) showed a pneumocycle in close proximity to the upper surface of the liver.



FIG 1 Case 1 (Upper left) A circular air containing cyst or pneumocycle is seen between diaphragm and liver on right side.

FIG 2 Case 1 (Upper right) Ballooning of pneumocycle with increased pressure. A Shadow of falciform ligament. B Pneumocycle.

FIG 3 Case 1 (Bottom) Deflated pneumocycle following decreased intra-abdominal pressure, showing indented, serrated outline.

#### DISCUSSION

The appearance of these abdominal pneumocycles may be readily understood if the various peritoneal surfaces and reflections of the upper abdominal cavity are considered.

The visceral peritoneum covering the anterior surface of the stomach is continued between the stomach and liver, forming the anterior layer of the lesser omentum. It next invests the inferior, anterior, and upper surface of the liver. At the posterior portion of the



upper surface, it leaves the liver and goes to the diaphragm to form the anterior layer of the coronary ligament. Proceeding further, the peritoneum covers the anterior part of the dome of the diaphragm and on reaching the anterior abdominal wall is continued as the parietal peritoneum of the general abdominal cavity.

The visceral peritoneum covering the posterior surface of the stomach extends from the lesser curvature to the liver thus forming the posterior layer of the lesser omentum. It continues upward, investing the posterior surface of the liver, and is then reflected onto the diaphragm to form the posterior layer of the coronary ligament. Thus, this portion of the omental bursa behind the liver, known as the superior recess, is in direct communication with the general abdominal cavity (greater sac) through the epiploic foramen.

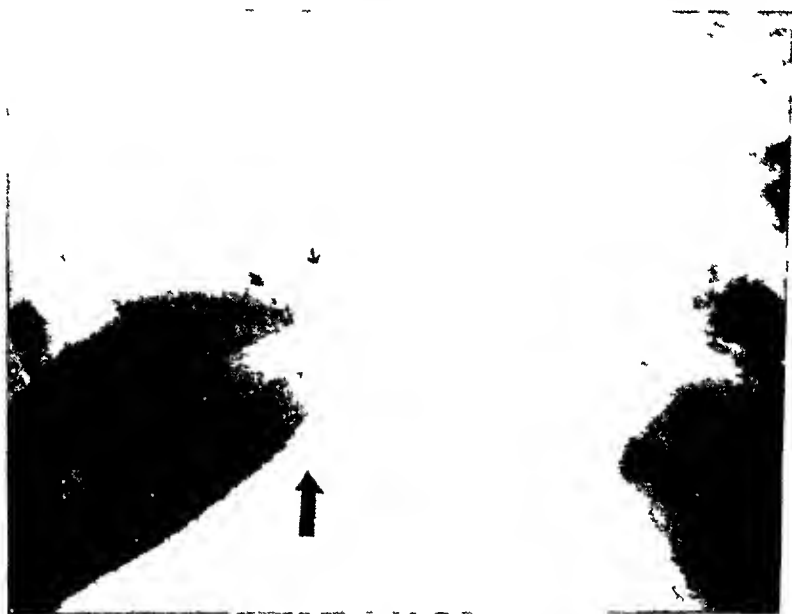


FIG. 4 Case 2 Pneumocoele just above upper surface of liver

The falciform ligament extends forward and downward along the anterior abdominal wall to the umbilicus as a peritoneal reflection from the anterior layer of the coronary ligament. This represents the anterior portion of the primitive ventral mesogastrium of the embryo.

From the above anatomical considerations of the peritoneal reflections of this sub-diaphragmatic area, it becomes evident that with the elevation of the diaphragm from the liver there must be a resultant stretching and thinning of these peritoneal ligamentous attachments. The lesser sac posteriorly and the greater sac anteriorly are in direct communication below via the epiploic foramen but are separated above by the transversely situated coronary ligament. The falciform ligament connects the anterior portion of the coronary ligament to the anterior abdominal wall, thus restricting posterior displacement of the transverse coronary ligament. There is, however, no such restricting mechanism to prevent anterior ballooning or displacement.

The anatomical explanation offered appears to be borne out by fluoroscopic examination of the cases presented. The ballooning is anterior in the direction of least resistance, and to the right of the falciform ligament wherein lies the greater expense of the right coronary ligament.

It is believed, therefore, that, dependent upon individual anatomical variation and upon differences in intra-abdominal pressure tensions upon the correspondent portions, the appearance of pneumoceles or peritoneal balloons may be expected in certain individuals receiving artificial pneumoperitoneum

## SUMMARY

1 The appearance of pneumoceles, or peritoneal ballooning, was observed in two cases receiving artificial pneumoperitoneum therapy for pulmonary tuberculosis

2 An anatomical explanation for the appearance of these pneumoceles is offered

## SUMARIO

*Neumocelos Abdominales Consecutivos al Neumoperitoneo Terapéutico*

1 En dos casos en que se aplicó el neumoperitoneo terapéutico por tuberculosis pulmonar, se observó la aparición de neumocelo, o inflamación peritoneal

2 Ofrecese una explicación anatómica de la aparición de esos neumocelos

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# PNEUMOPERITONEUM COMPLICATED BY INGUINAL HERNIA<sup>1</sup>

## Report of a Case

WILLIAM J. McAULIFFE AND RICHMOND DOUGLASS

(Received for publication April 11, 1949)

Therapeutic pneumoperitoneum as a form of immobilization of the tuberculous lung has been used widely since 1935. The procedure is simple and the complications are few. Banyai (1) discusses air embolism, accidental pneumothorax, and mediastinal emphysema and mentions the appearance of pneumocele and coexistence of hernia among miscellaneous complications. Bennett (2) in 1938 reported discontinuing pneumoperitoneum in 3 cases because of the appearance of hernia. Monto and Bradford (3) in 1943 reported a case of pneumocele following pneumoperitoneum. The pneumocele was treated by the application of a pressure pad over the internal inguinal ring after the air had receded from the processus vaginalis. Apparently the pressure caused obliteration of the sac for the pneumocele did not reappear on subsequent refills. Daniels and Eisele (4) in 1938 mentioned 2 cases with inguinal hernia in whom scrotal pneumocele developed following pneumoperitoneum. These were treated with trusses.

A case of inguinal hernia treated surgically is reported because of the limited mention of hernia as a complication of pneumoperitoneum and because no report of surgical treatment has been found after intensive search.

A. R. (BMH 37025), a 25-year-old, single, white female was admitted by transfer from another hospital to the Hermann M. Biggs Memorial Hospital on October 28, 1948 for continuation of treatment for pulmonary tuberculosis which was moderately advanced and was active. The history revealed the onset of illness in January 1938 and the clinical course was characterized by recurrent hemoptyses and repeated hospitalizations, during which she was on a variety of therapeutic regimens. In May 1948, with cavity present on the left and a sputum positive for *M. tuberculosis*, pneumoperitoneum, supplemented by crushing of the left phrenic nerve, was instituted and maintained with weekly refills of 1,000 cc. Immediately after the induction of pneumoperitoneum the patient noticed a small lump in the right groin which had a peculiar "crackling" feel. Coughing, sneezing, or straining in any way caused the lump to become prominent but it always receded with relaxation. These findings were confirmed by her physician, but no treatment was instituted.

On admission to the Hermann M. Biggs Memorial Hospital, the physical examination revealed an asthenic, pale, thin, young adult, white female lying quietly in bed. The positive physical findings were limited to the chest and abdomen. There were post-tussive crepitant rales in the right apex and slight abdominal distention with absence of liver dullness. Routine examination revealed no abnormality in the right groin.

Fluoroscopy and roentgenograms of the chest revealed paradoxical motion of the left diaphragm which was at the level of the fourth anterior rib, and showed a normally functioning right diaphragm at the level of the fifth anterior rib. There was also noted scattered infiltration in both hilar regions.

**Laboratory data.** The erythrocyte and leukocyte counts were within the range of normal, and examination of the urine revealed no abnormal findings. There was no sputum for examination. Cultures of the gastric washings taken on admission were negative for tubercle bacilli.

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<sup>1</sup> From the Surgical Service, Hermann M. Biggs Memorial Hospital, Ithaca, New York.

On November 3, 1948, six days after admission, the patient complained of a slightly painful lump in the right groin. Examination revealed an irreducible right indirect inguinal hernia. She was placed in Trendelenburg position with hot water bottles to the abdomen and given 10 mg. of morphine. After a few hours another attempt at taxis was successful. The hernial sac filled with air, however, and a lump in the groin persisted. It was believed that pneumoperitoneum would aggravate the condition and that strangulation might occur. Because of the universally satisfactory response of congenital inguinal hernia to surgery (5), operation was decided upon.

Under spinal anesthesia a 10 cm. incision was made above the right inguinal ligament. The external spermatic and cremasteric layers were opened, exposing the sac of an indirect inguinal hernia lying anteromedial to the round ligament. The sac, which contained air but no bowel or omentum, was transected without opening and the proximal stump ligated with a suture ligature of number 00 black silk after it had been tightly twisted. The distal portion of the sac was found to extend down to the insertion of the round ligament and included a tiny hydrocele. The hernial defect was then repaired according to the Ferguson technique. The wound healed per primam, the skin sutures being removed on the fifth postoperative day. Pneumoperitoneum refills were resumed on the fourteenth postoperative day.

This case illustrates the conversion of a congenitally patent processus vaginalis to a pneumocele following induction of pneumoperitoneum, with eventual herniation of abdominal viscera. Surgical repair was preferred to the method of pressure over the internal ring. Pneumoperitoneum and pulmonary tuberculosis were not regarded as contraindications to operative repair, particularly with the use of spinal anesthesia. Hemorrhaphy was, therefore, done and pneumoperitoneum continued.

#### SUMMARY

1 An inguinal pneumocele appeared in a 25-year-old woman immediately after induction of pneumoperitoneum.

2 A right inguinal hernia which was reduced with difficulty occurred six months later.

3 Repair of the hernia was carried out under spinal anesthesia without interrupting the therapeutic pneumoperitoneum and without adverse effect on the patient's clinical course.

4 Pneumocele occurring in the inguinal region during pneumoperitoneum indicates a congenitally patent processus vaginalis and, since this is amenable to surgery, operative repair is indicated.

#### SUMARIO

##### *Neumoperitoneo Complicado con Hernia Inguinal. Observación*

1 En una mujer de 25 años se presentó un neumocelo inguinal inmediatamente después de ejecutarse un neumoperitoneo terapéutico.

2 Seis meses después apareció una hernia inguinal derecha que fué reducida con dificultad.

3 La hernioplastia fué llevada a cabo con raquianestesia sin interrumpir el neumoperitoneo terapéutico y sin efecto adverso sobre la evolución clínica del caso.

4 La aparición de un neumocelo en la región inguinal durante el neumoperitoneo indica la existencia de un proceso vaginal congénitamente permeable, y como puede ceder a la cirugía, está indicada una operación plástica.

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## EDITORIAL

### The Cost of Tuberculosis Research

Elsewhere in this number of the American Review of Tuberculosis is an article by Virginia Cameron, Medical Research Secretary of the National Tuberculosis Association, in which an analysis is made of the cost of research on tuberculosis for a twelve-month period in 1947-1948. The report is objective and no attempt is made to determine whether the amount is inadequate or excessive, or if the results of the researches financed in that year justified their cost. The analysis does show, however, that the current annual expense for conducting research on tuberculosis in the United States exceeds six million dollars, that the majority of the sum currently spent is in the field of chemotherapy, and that the two chief contributors to the total cost are the Federal Government and industrial firms engaged in the production of pharmaceuticals.

It is not surprising that the total amount of money spent on tuberculosis research is large. In terms of lives lost, tuberculosis has been the most destructive disease in all history. Recovery from the disease, however, is as astonishing as its ravages, and the circumstances under which recovery occurs have stimulated an immense amount of investigation, ranging in the past from the most critical to the utterly absurd in efforts to develop a consistently successful means of control or cure. In their sum these efforts have been notably productive, if still falling far short of their goal.

Until relatively recently little of this research has been sponsored or stimulated by other than individual original interest. Personal interest, however, has always been a powerful source, and the governmental and organizational support characterizing the present period could accomplish little without the spontaneous spirit of inquiry of individual investigators.

A brief review of past achievements will show that every development in the control of tuberculosis has resulted from research. Understanding of the fundamental nature of the disease came from a long series of patient anatomical studies by Sylvius, Laennec, and scores of less well-known investigators. Their studies in turn paved the way for the discovery of physical diagnostic methods by Auenbrugger, Corvisart, and Laennec, and the immense amount of detailed clinical investigation which followed. The development of experimental medicine, to which Claude Bernard contributed so notably, and of bacteriological methods by Augustino Bassi and Jacob Henle and their early associates, opened the road for the specific investigations on tuberculosis by Villemin and Koch. In a purely physical investigation William Conrad Rontgen discovered X-rays, but within a few months surgeons applied the discovery to clinical medicine, and chest X-ray photography was a natural development.

It must not be forgotten, however, that each major discovery in medicine has resulted only through the summation of a vast number of major and minor discoveries in the same and quite different fields. The tubercle bacillus would not have been discovered without the microscope and the microscope could not have been invented and improved without exhaustive physical and mathematical in-

vestigation of refracting lenses X-ray photography would be impossible without suitable light-sensitive materials, which did not become available purely by accident. Modern laboratory and clinical diagnosis of tuberculosis, its sanatorium, surgical and chemotherapeutic treatment, and the facts of epidemiology and public health, all have resulted from a synthesis of a huge amount of research. Chance entered into many important observations, but exact investigation has always been the next step after a lucky accidental find.

The productivity and ultimate value of medical research are seldom in direct proportion to its cost. Many of the greatest discoveries have been at little expense. Jenner's development of smallpox vaccination was of small cost to himself and none to any sponsoring agency. The outstanding investigation in the history of tuberculosis, the discovery of the tubercle bacillus, was made in the course of the normal duties of a section chief in the German Imperial Department of Health, Robert Koch. His personal industry and unquenchable curiosity, and the recently acquired background in bacteriological method which he had himself done much to develop, resulted in this major event in the history of tuberculosis without proportionate cost. Interestingly enough, had he not discovered the tubercle bacillus, little delay in its detection would have occurred, for Paul Baumgarten was but a few steps behind him and actually did report his own discovery a few days later. Confirmation of the studies of the two men came quickly from many sources, and again at little cost. Simple laboratory procedures for the detection of the tubercle bacillus in sputum and other pathological material were soon developed and readily available throughout the world.

In contrast, certain other and equally important fields have had to be cultivated on a much more expensive scale to yield comparable results. Perhaps no tool is more valuable in the diagnosis and care of tuberculosis than the X-ray. Millions of dollars have gone into the development and improvement of X-ray equipment since Röntgen's discovery of the ray a little more than fifty years ago. In view of the enormous value of X-ray photography in tuberculosis, the great cost has been well warranted. The far cheaper development of bacteriological diagnosis has been simply a happy circumstance.

The cost of all scientific research is rising and probably in greater degree than costs in general. The Curies' discovery of radium was at trifling expense compared with the cost of current investigations on nuclear fission. Extremely expensive equipment is essential for new advances in this field, and progress in other fields, including the development of new knowledge of disease, is analogous in its demands for better tools and methods. It is trite that research stimulates new research, but it is perhaps not so widely appreciated that the new research will almost always be more expensive than the old.

It has been suggested from time to time that some slackening in the general program of research on tuberculosis might now be justified, since progress up to date, as measured by the declining death rate, seems to indicate that the disease can be brought under complete control by procedures presently at hand. This is surely a short-sighted view of the future. No sufferer from the disease undergoing a long and tedious sanatorium course, even supported by daily injections of

streptomycin, is likely to be solaced by statistics if his own progress is doubtful, and no economist viewing the present annual hundred million dollar cost of sanatorium and hospital care of tuberculosis will be satisfied that no further investigation is needed. There may and should be argument as to the direction new research should take, and particularly as to the relative proportions of developmental, basic, and applied investigation, but adequate perspective will convince every thoughtful observer of the need for improvement in methods, and there is no escape from the fact that all improvements, in their very nature, result from some kind of research.

It could well be argued, however, that a large sum, greatly exceeding present expenditures, might be used still more profitably to speed up the present apparently productive program. Something of this character has been suggested by the National Planning Association (Planning Pamphlet No. 62, *Good Health is Good Business*, Section 1, *Tuberculosis: Why not get rid of it?*). The plan proposed calls for universal X-ray examination, expanded facilities for treatment, improved health education, and a large rehabilitation program. Attention has been called to some of the difficulties inherent in operation of the plan (Dempsey, Mary, *Summary of Review of National Planning Association's Report*, National Tuberculosis Association, September 28, 1948), but it is noteworthy that even this plan calls for an expenditure of \$3,000,000 a year for research in a ten-year program requiring an outlay of \$321,000,000 a year in its peak years.

Detailed suggestions are not made in that plan as to the distribution of the \$3,000,000 designated. The proposal for this sum is based on an estimated expenditure of \$1,200,000 for tuberculosis research in 1943, an amount greatly exceeded by the actual expenditures for tuberculosis research in twelve months of 1947-1948, as Miss Cameron's analysis indicates. Presumably the figure was intended to be elastic, as medical research is opportunistic, as is well illustrated by trends in tuberculosis research since the advent of streptomycin.

It is impossible to avoid being arbitrary in naming any sum as appropriate for a tuberculosis research program. There appears to be some justification from industrial experience in the figure of one per cent of the national income set by Mr. John R. Steelman, Chairman of the President's Scientific Research Board, in his *Report to the President* as a "modest annual investment" for a national program of scientific research. This figure has proved a useful one for planning, and it may be noted in this connection that it has been employed by the National Tuberculosis Association in its own estimate of expenditure for research on tuberculosis.\* The NTA estimate is not purely arbitrary, however, for it was based in large part on the fact that the present expenditure of the Association is less than that sum, while promising projects go unsupported for lack of funds.

It would seem wise for planning purposes to set up figures of as much signifi-

\*The following resolution was adopted by the Board of Directors of the Association at its meeting on May 2, 1949: "Resolved, that commencing with the 1950 Seal Sale contract the proportion of Seal Sale funds allocated to the NTA shall be increased to six per cent, [from five per cent] one sixth of which shall be allotted to the research program of the NTA."



cance as possible on the basis of recent experience in the several individual federal, industrial, foundation, and academic programs. Suitable estimates for this purpose could hardly be made without an analysis of current expenditures for research, indicating costs, sources of financial support, and types of investigation financed. Miss Cameron has presented such an analysis, which should be of great value at a time when interest in the investigation of tuberculosis is increasingly active and organizations like the Public Health Service and the National Tuberculosis Association are expanding their programs in this field.

Certain reservations must be made in accepting the figures cited, as Miss Cameron herself has indicated. As an example, the cost of research in large industrial firms will vary with systems of accounting employed, and it is difficult or impossible to estimate the research expenditure involved in the salaries of workers who collect new facts from daily routine experience. The research element in the large mass X-ray surveys now in operation cannot be calculated without full knowledge of the use made of the figures obtained. This knowledge is not available and hence a research cost cannot be estimated. Such surveys are primarily for case-finding purposes, but their results when properly analyzed are of great value for epidemiological understanding and further planning, and it would be logical to designate a portion of the cost as for research if all facts were known.

It is significant that the donors of the largest sums for investigations, the official health agencies and the manufacturing firms, contributed a high percentage of the total allocated for a single purpose, streptomycin research. If streptomycin had not appeared so promising it is safe to say that much less money would have been expended for chemotherapeutic research, and much less accordingly for all tuberculosis research, since the proportion of the total cost for chemotherapy alone in 1947-1948 was so high.

It is equally significant that organizations long concerned with basic and developmental investigations, *i. e.*, scientific foundations, the National Tuberculosis Association, its affiliates, and the universities, have continued to devote the majority of their resources, presumably in spite of many pressures when applied chemotherapeutic research is so alluring, to fundamental research. At the present time increasing emphasis on the need for new fundamental research is widespread. Had streptomycin proved as successful as the most optimistic enthusiasts anticipated, had it proved, for example, as effective as penicillin in certain types of pneumonia, it is probable that interest in basic investigation on tuberculosis would have declined. Actually, however, streptomycin research has raised more problems than it has answered, and the new problems, such as the nature of the antibiotic mechanism and the reason for bacillary resistance to the drug, can be solved only by fundamental laboratory research.

Similarly the recent numerous empirical studies on BCG vaccination, while indicating the practical value of the procedure, have brought to the front, as never before, the necessity for further studies on the virulence of acid-fast bacteria and the whole problem of pathogenesis. There is indeed good reason to believe that unless more powerful substitutes for streptomycin are found and BCG vaccination proves more widely effective than present conservative investi-

gators believe it to be, the investigative trend in both fields will be toward basic rather than applied research

For these reasons it may well be that the current distribution of research effort, as revealed in the report by Miss Cameron, will not be representative of future periods. Her analysis provides, however, the perspective needed for evaluation of the present program in terms of its cost, and a good basis at the same time for future planning

ESMOND R. LONG

## LETTERS TO THE EDITORS

### WHAT'S WRONG WITH "MASS X-RAY" SURVEYS?

*To the Editors of the American Review of Tuberculosis*

Recent statements by Doctor James F Brailsford, the eminent British radiologist, have raised some doubts in the minds of many as to the real value of community-wide surveys. At first glance it is easy to ridicule Doctor Brailsford's thesis and we may even fall into that common habit of Americans of believing that just because we do things in a certain manner in this country it is of course the only way to do it! A few of us in Tuberculosis Control, however, are not so sure that everything is peaches and cream in Georgia. We are even convinced that Doctor Brailsford may be partially correct, and what's more, not being content to just talk about it, we'd like to do something about it.

First, we're going to tell a little story (Albrecht, F K Editorial in *Current Medical Digest* (April) 1949) and we'll let you be the judge.

John Doe reads in his newspaper, "Get your free X-ray at the George Washington School Building tomorrow between 8 and 10 a m." Unfortunately the use of the term "free x-ray" is false, since it is being furnished by the State Board of Health and only because John Doe's taxes have helped to purchase the equipment.

John Doe enters the lineup of folks awaiting their X-ray at the school building and when he reaches the registry desk, who should be typing the registry cards but his next door neighbor, Mrs Jones. She greets John and asks "Is there any tuberculosis in your family?" This information is, of course, requested for good reason on the registry card. Terror strikes John's heart. Both his parents died in a sanatorium of tuberculosis, but if he says "Yes," little Mary, Mrs Jones's daughter, will not be allowed to play with little Willie any more. And so he gulps "No" and stumbles away in confusion. What if the film does show tuberculosis? Will the neighbor's wife find out? Maybe she will see the cards when they are ready to be mailed out to those X-rayed! The whole neighborhood will be talking and John is in an extreme state of confusion. The film reader is being paid so much per film, instead of a flat fee per hour and, even though he is a bit fatigued, he reads on and on and on until he comes to the 70 mm film of John's chest. Either inadvertently, or because he doesn't know of the distortion inherent in small film, he calls it a "Cardiac." It really isn't enlarged at all. What happens now? John's survey card is marked "Cardiac." About six weeks later, the local Tuberculosis Society announces in the paper that all the negative cards for the recent survey have been mailed. John Doe becomes worried and sick with fear. Does he have tuberculosis? He must have, since he has not received a negative card! Has he infected little Willie and his loving wife? Does the next door neighbor know? It seems she has acted a bit distant lately.

John Doe does one of two things. Disconsolate and frustrated he goes to a roentgenologist and pays \$15, which he can ill afford, for a large film. After a few days he is told "There is nothing wrong with you." Failing this procedure, our John sweats it out for a few weeks and finally receives the little card telling him to see his doctor, who also advises a large film, which this time however is paid for by the local Tuberculosis Society. Two more weeks transpire before the film is read and finally the news arrives "Film of poor diagnostic quality—will require a retake." The doctor in the meantime has assured him that there was no tuberculosis in the film—"Just a heart condition!" What are the chances of John's becoming a cardiophobe? How would you feel? Or, suppose the film reader in all sincerity noted "Scoliosis, severe," or "Dextrocardia," or "Pulmonary fibrosis, cause undetermined?" What can be done about it?

What is our solution? Education, or should we say re-education. We must educate the general public who seem to know little if anything about tuberculosis except a lot of misconceptions they have picked up in school under the subject of Health Education. They have the feeling that by some remarkable gift or innate inherited power they alone will never contract the disease. They believe that you conquer disease by dropping a dime or a quarter in a tin can on a street corner, and, of course, by buying Christmas Seals. Why should they worry? Tuberculosis is something only poor people get and they hear it is almost wiped out.

Is it any wonder the general public may develop a phobia and fear toward being X-rayed? They are told absolutely nothing. All agree that they should not be sent the findings of the small film since the medical terms used would only terrify them. They should be told, however, that there are many reasons *other than disease* that may cause one to be called back for a large film. If the general public knew these things, there would not be the fear and terror occasioned when that fateful card arrives saying "See your doctor."

The introduction of mass chest radiography to the civilian population is no easy undertaking. It must be done without causing fear and anxiety in those found to have suspicious shadows in their chest films. It must also be done without inducing a false sense of security in those who are shown to have a normal chest film.

In a recent book *Photoradiography in Search of Tuberculosis* (Zacks, D., Williams & Wilkins, Baltimore 1949), Dr. David Zacks of the Massachusetts Department of Public Health presents his experiences covering twenty years in tuberculosis control. He raises the question as to the real worth of the so-called "fast tempo" surveys, wherein after a lot of publicity and ballyhoo a whirlwind campaign is carried on for a short time, after which it moves on like a traveling road show to another community, leaving in its wake and in the local health officer's lap a multitude of problems, headaches, and heartaches.

I quote from Dr. Zacks' text:

The high pressure campaign technique requires multiple X-ray units, adequate technical and professional personnel and sufficient financial resources with ability for rapid community organization and high pressure publicity in order to arouse not only interest in the community, but also a willingness to participate personally in the X-ray program. The campaign approach is rapid, spectacular, and high-g geared but its contribution to tuberculosis control may be equally fleeting. The author prefers the relatively slow, sustained, systematic attack upon the problem.

The plan proposed is based upon extensive community organization and adequate chest diagnostic facilities, in addition to the survey procedure.

In order to bring about individual acceptance of the (chest) examination, education regarding pulmonary tuberculosis is necessary. The educational program must be continuous and purposeful in order to influence people.

There is no question here of socialized medicine. Mass chest X-ray examination is an ethical attempt to get at the root of tuberculosis control. To attain this aim it must include the total population rather than groups chosen for accessibility or a willingness to participate.

The ultimate aim is the establishment of chest X-ray service which will be available on a permanent basis to all persons, either through private physicians, health departments or cooperating community health agencies. The attainment of these objectives will depend in large measure upon education, not only education of the people themselves but also education of official and voluntary health agency leaders.

No community-wide chest roentgenographic survey can be considered satisfactory unless it permits a correct diagnosis. All agree that the small films are for screening purposes only and that it is essential to secure a 14 by 17 film and a clinical history for ten-

tative and differential diagnosis Yet it is extremely rare indeed for physicians to supply any clinical history or information with the large follow-up films they send in for interpretation Thus the program is still a screening program There is no excuse for failure to supply a very short history with 14 by 17 films Any nurse or office technician should be able to elicit a short, concise, pertinent history from a patient Since a large majority of 14 by 17 follow-up films sent in for interpretation are not of diagnostic quality one concludes that either John Q Patient or the Tuberculosis Associations are paying thousands of dollars yearly for worthless films

There is need to re-educate some of the medical profession A good physician recognizes the limitations of his stethoscope and will not try to diagnose tuberculosis with it He appreciates that one can appear hale and hearty and have clinical tuberculosis If he is told that a suspicious shadow was found on the 70 mm film and is advised to have the patient get a large film, he will not scoff at such advice or tell the patient there is nothing wrong with him He will know his own limitations in reading large film and not be ashamed to seek advice and counsel from his colleagues if he has had no special training in such film reading He will never make a diagnosis based only on shadows If he does not wish to do the necessary follow-up measures, it is his privilege to solicit the aid of a private consultant or to turn it over to public health authorities He should not expect a diagnosis from a roentgenologist or film reader based on some shadows on celluloid without furnishing a short provisional diagnosis or clinical history He should try to furnish films of diagnostic quality if he expects a diagnosis He will report his cases to the proper health authorities Before criticizing community-wide surveys and declaring they are a step toward State medicine, he will ask himself Am I really concerned with the health of all people, including the indigent, in my city or county? He will remember that the first 14 by 17 film is still a screening film and that it is needed by the official agency conducting the survey to check its small film findings and complete the necessary records It does not mean that he or several other physicians in his community are not capable of reading film He must appreciate that "overreading" of small film, while it can cause great concern to those notified to see their physician, is better than underreading, if we are to pick up early treatable tuberculosis He will be careful not to unduly alarm his patients as a result of some congenital abnormality reported on the small film He will recognize his responsibility, examining his patients who are contacts of known open cases He is entitled to his opinion and criticism of mass roentgenographic surveys, but before he lends his voice to such proposals as the restriction of surveys in his community to school children only, he should either examine his conscience or buy some new medical books!

Proper steps should be taken to re-educate our small film readers They should approach this task with due respect and be mindful of the havoc they can create by insufficient training or bad judgment They should be very cautious about reporting enlarged hearts or telling a person to see his doctor because of some condition he has lived with for sixty years such as scrobosis or fibrosis What can either the doctor or patient do about it? It is this kind of stupidity that is bringing down opprobrium on these community-wide programs For this reason alone there should be an A and B reader employed to read small film It may be costly but it would reap large dividends in less worry and needless anxiety which is caused by overreading

Maybe we directors can also stand a bit of re-education Before criticizing the voluntary workers, the general practitioners, and others connected with these programs, we should ask ourselves whether we have done all in our power to help these people We will hold seminars for the voluntary workers, dispel their confusion, and correct their mis-

conceptions. If they know what to do and why they are doing it, they will do better work. We will seek every opportunity to address County Medical Societies both before and after the units enter their locality, so as to clear up the many problems that may arise following such surveys.

The Tuberculosis Control Division of the state of Kansas has inaugurated a plan wherein the actual 70 mm. film is sent to the family physician on all cases with significant findings. The physician thus has the small film in his possession on which the suspicious area is indicated with a China pencil. He can keep it with the patient's record and it may prove of valuable use in later years as a base line study. This is a step forward in educating our physicians, many of whom are skeptical about the value of small films.

Is this a big order? We think so, but we are sure there will be many who are glad to take up the challenge.

DIVISION OF TUBERCULOSIS CONTROL  
KANSAS STATE BOARD OF HEALTH  
TOPEKA, KANSAS  
June 27, 1949

F. KENNETH ALBRECHT,  
DIRECTOR

## LETTERS TO THE EDITORS

### ROENTGENOGRAMS OF DIFFUSE PULMONARY LESIONS

*To the Editors of the American Review of Tuberculosis*

I have been interested for some time in the diffuse pulmonary lesions which may give roentgenographic shadows resembling those of miliary tuberculosis. We had a small exhibit dealing with this subject at the last meeting of the National Tuberculosis Association in Detroit. Enough doctors have shown an interest in the problem to tempt me to go on and try to collect still further examples of this often very confusing situation.

At the present time I have listed the following conditions as capable of giving the diffuse type of lesion that I have described. I am sure that this list is not yet complete.

#### I INFECTIONS

- a Tuberculosis\*
- b Bacterial
  - 1 *Streptococcus*\*
  - 2 *Staphylococcus septicemia*
  - 3 *Brucellosis*
  - 4 *Tularemia*
- c Mycotic
  - 1 *Momhasis*\*
  - 2 *Aspergillosis*
  - 3 *Coccidioidomycosis*
  - 4 *Actinomycosis*
  - 5 *Blastomycosis*
  - 6 *Histoplasmosis*
  - 7 *Torulosis*
- d Rickettsial
  - 1 *Q fever*
- e Virus
  - 1 "Atypical pneumonia"
  - 2 *Psittacosis*
  - 3 *Varicella*
- f Parasitic
  - 1 *Schistosomiasis*

#### II INHALATIONS

- a Industrial
  - 1 *Silicosis*\*
  - 2 *Asbestosis*\*
  - 3 *Beryllium*\*
  - 4 *Siderosis*\*
  - 5 *Bagassosis*
  - 6 *Byssinosis*
  - 7 *Vanadium*
  - 8 *Silver*
  - 9 *Talc*
  - 10 *Aluminum*
  - 11 *Barium*
- b Other
  - 1 *Vomitus*\*
  - 2 *Lipiodol*\*
  - 3 *Kerosene*
- c Thermal

## III NEOPLASMS

- a Primary
  - 1 Bronchogenic carcinoma\*
  - 2 Alveolar carcinoma\*
  - 3 Pulmonary adenomatosis
- b Metastatic
 

1 Stomach*	7 Thyroid
2 Liver*	8 Breast
3 Prostate*	9 Pancreas
4 Melanotic sarcoma*	10 Ovary
5 Hypernephroma	11 Uterus
6 Tongue	12 Chorioma
- c Generalized
  - 1 Lymphoma
  - 2 Reticulum-cell sarcoma\*
  - 3 Multiple myeloma

## IV BLOOD DISEASES

- a Myelogenous leukemia\*
- b Polycythemia vera
- c Sickle-cell anemia

## V GENERALIZED DISEASES

- |   |  |
|---|--|
| <ul style="list-style-type: none"> <li>a Sarcoidosis*</li> <li>b Erythema nodosum*</li> <li>c Rheumatic fever</li> <li>d Lupus erythematosus disseminatus</li> <li>e Periarteritis nodosa*</li> <li>f Loeffler's syndrome*</li> </ul> | <ul style="list-style-type: none"> <li>g Tropical eosinophilia*</li> <li>h Cystic disease of the pancreas*</li> <li>i Xanthomatosis</li> <li>j Amyloidosis</li> <li>k Scleroderma</li> </ul> |
|---|--|

## VI FIBROSIS—GRANULOMATOSIS—BRONCHIOLECTASIS

- |   |   |
|---|---|
| <ul style="list-style-type: none"> <li>a Fibrosis*</li> <li>b Granulomatosis*</li> <li>c Bronchiolectasis*</li> </ul> | <ul style="list-style-type: none"> <li>d "Acute interstitial fibrosis"</li> <li>e Bronchiolitis fibrosa obliterans</li> </ul> |
|---|---|

## VII CIRCULATORY DISTURBANCES

- a Pulmonary edema\*
- b Hemosiderosis\*
- c Emboli and infarcts
  - 1 "Phlebitis"\*
  - 2 Lipidol\*
  - 3 Fat

The starred diagnoses in the above list are the conditions of which I already have a good example, and most of these roentgenographic reproductions were shown in the 1949 Exhibit

I am anxious to get good examples of the conditions in the above list which are not starred or of any other conditions of which other doctors may have examples. I thought you might believe it worth while to publish this letter in the American Review of Tuber-



eulosis to inform the men particularly interested in respiratory diseases throughout the country that we are trying to increase our collection of examples of diffuse pulmonary lesions and, if they have a roentgenogram of the type of case for which we are looking, I would appreciate it very much if they would mail the film to me with a very brief summary of the case and a statement of the test which proved the diagnosis given. We will then have a transparency made from the film and return the film itself to the sender. We will include the transparency in next year's exhibit and of course give credit to the man sending the film to us.

1101 BEACON STREET  
BROOKLINE, MASS  
June 23, 1949

DONALD S. KING

## LETTERS TO THE EDITORS

### ON THE ACTION OF THIOSEMICARBAZONES IN EXPERIMENTAL TUBERCULOSIS IN THE MOUSE

*To the Editors of the American Review of Tuberculosis*

The antituberculous action of a number of thiosemicarbazones was first noted by Domagk, Benisch, Mietzsch, and Schmidt (Naturw, 1946, 10, 315) in 1946, and preliminary clinical trials in man were described by Moncorps and Kalkhoff (Med Klin, 1947, 42, 812) in the following year. Recently several reviews in the German literature have included descriptions of the activity and pharmacology of some of these compounds (Heilmeyer, von L. Deutsche med Wchnschr, 1949, 74, 161, Vinderbank, H. Die Pharmazie, 1949, 4, 198). Apparently the antituberculous activity of these compounds has not yet been given serious consideration in this country.

One of these compounds, *p*-formylacetanilide, 3-thiosemicarbazone

$$\left( \text{CH}_3\text{CONH}-\text{C}_6\text{H}_4-\text{CH}=\text{N}-\text{NH}-\underset{\text{S}}{\underset{\parallel}{\text{C}}}-\text{NH}_2 \right),$$

has been studied *in vitro*, as well

as *in vivo*, in the mouse in our laboratories. In a modified Kirchner's medium, containing Triton A-20 (a dispersing agent), the minimal inhibiting concentration for BCG was 0.0008 mg per ml. In the mouse the maximal acceptable dose in the diet was found to be 0.032 per cent giving a daily dose of approximately 65 mg per Kg per day.

When administered at this maximal acceptable dose in the diet for 21 days to mice infected intravenously with the Ravenel strain of *M. tuberculosis* in a highly standardized test (a) McKee, C. M., Rake, G., Donovanick, R., and Jambor, W. P. Am Rev Tuberc, 1949, 60, 90, (b) Donovanick, R., McKee, C. M., Jambor, W. P., and Rake, G. Am Rev Tuberc, 1949, 60, 109, (c) Rake, G., Jambor, W. P., McKee, C. M., Pansy, F., Wiselogle, F. Y., and Donovanick, R. Am Rev Tuberc, 1949, 60, 121), deaths did not begin to appear until almost 40 days after infection, whereas all controls were dead before the thirtieth day. The minimal dose causing significant increase in  $T_{50}$  (50 per cent death time) was found to be approximately 0.004 per cent in the diet (equivalent to approximately 8 mg per Kg per day) when treatment was started two days before infection.

Thus far, delayed treatment has been tried in only one experiment in which a level of 0.016 per cent in the diet (equivalent to approximately 32 mg per Kg per day) was used. It was found that the compound was highly active at this level even when treatment was not started until 7 days after infection, and possibly active even when administration was delayed until 14 days post infection, in a test in which the  $T_{50}$  of the controls was 177 days, and some deaths had already occurred on the thirteenth and fourteenth days.

It is not possible at the time of this preliminary report to give a quantitative comparison between the action of this compound and other antituberculous compounds such as *p*-aminosalicylic acid. However, an indication may be obtained by noting that at 0.75 per cent in the diet, *p*-aminosalicylic acid gave  $T_{50}$  values of 240 and 300 days, respectively, in two tests in which the thiosemicarbazone was tested. In these tests the latter compound at 0.016 per cent in the diet gave  $T_{50}$  values of 35 and 45 days, respectively.

Extensive studies on the toxicology and pharmacology of this and related compounds are now under way in these laboratories.

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# THE AMERICAN REVIEW OF TUBERCULOSIS

## ABSTRACTS

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### CLINICAL STUDIES, TUBERCULOSIS

**Tuberculosis in Children**—Because of the diverse opinions regarding the proper management of tuberculosis in children, the courses of 234 patients hospitalized between 1912 and 1947 were reviewed. The ages ranged from five months to thirteen years. The criteria for admission were (1) a positive tuberculin test, and (2) roentgenographic evidence of an active pulmonary or tracheobronchial lymph node lesion. On admission 79.5 per cent were diagnosed as having primary tuberculosis, 9 per cent had pleurisy with effusion, 6 per cent had miliary tuberculosis, 3 per cent had the reinfection type of tuberculosis, 2 per cent were nontuberculous, and one patient had tuberculous meningitis without a demonstrable pulmonary lesion. Of those with a primary infection, 89.8 per cent were asymptomatic and 89.3 per cent were afebrile. Only 17 patients (9 per cent) were considered to be chronically ill and 8 of these had a serious nontuberculous infection. Acid-fast bacilli were demonstrated in 20.4 per cent of this primary group. Six patients in the primary group developed tuberculous complications after admission and 3 were readmitted for complications after discharge. The average hospital stay was 250 days. Treatment consisted of a general, high caloric diet, cod liver oil, feosol tablets and complete bed rest. Restraining jackets were used on young children considered to be too active. The children of school age were allowed one hour daily of classwork. None of the children with a primary infection received specific therapy in any form and no streptomycin was used. Children were considered

ready for discharge when there had been complete absorption of the parenchymal lesion and contraction or calcification in the regional lymph nodes. The hospitalization of these patients seems to offer only one advantage, the opportunity to diagnose a tuberculous complication in its early stages. This responsibility can well be taken over by the chest clinic—*Tuberculosis in children*, S. L. Painter, *Dis of Chest*, March, 1949, 15:329—(E. A. Rouff)

**Initial Pneumothorax**—A new technique was devised to minimize the trauma during the induction of pneumothorax. A 2 cc or 5 cc syringe is fitted with a sharp, short-bevel, small needle. The syringe is half filled with either saline or procaine solution. The needle is advanced just through the skin and the plunger drawn back to be sure the connections are air-tight. No bubbles must appear in the fluid. The patient is then instructed to hold his breath in deep inspiration while the needle is advanced. Constant suction is maintained with the syringe until a few bubbles appear in the fluid. The needle is then immediately withdrawn. The bubbles have come from the superficial alveoli, and leakage of air from these alveoli into the pleura will continue for a varying period to produce a pneumothorax space. Occasionally insufficient air escapes to produce a visible space. In this event the procedure should be repeated. If several attempts fail to establish a pneumothorax, the pleural space has been previously obliterated. Comparison of this new technique with the present manometric method reveals that the initial, traumatic collapse was approximately half as

great when the new procedure was used. Furthermore, there were fewer instances of excessive, dangerous collapse—*Initial pneumothorax. A new safe induction technique*, I J Selikoff, I G Tchertkoff & E H Robitzel, *Quart Bull, Sea View Hosp*, July, 1948, 10 93—(K T Bird)

**Follow-up of Collapse Therapy**—The fate of 94 patients who responded poorly to collapse therapy and one year's bed rest was traced during a follow-up period of five to twenty years. The mortality figures indicate the poor prognosis of those patients whose illness follows its course in an uncontrolled manner. Fifty per cent were alive after three years, 25 per cent after six years, and 10 per cent after ten years. These figures are in contrast to those of Duggelis, who compiled statistics from the same sanatorium on 486 patients whose sputa were negative for tubercle bacilli prior to discharge. Of these, 75 per cent were still living sixteen years later as compared with 3 per cent in the first group of poorly controlled patients—*Ergebnisse der Kollapstherapie bei schweren Lungentuberkulosen*, H Hasler, *Schweiz Ztschr Tuberk*, 1949, no 1 1—(E Dunner)

**Basal Tuberculosis**—Of 1,379 known cases of tuberculosis, 21 (1.52 per cent) were found to have had a characteristic basal onset of their disease. The short interval between onset and diagnosis, averaging 30.6 days, with extension of the lesion to a moderate or far advanced stage in all cases during this interval, and the roentgenographic characteristics indicate that reinfection tuberculosis with a basal onset should be classified as an acute and progressive disease. The average age of the 21 patients was 25.1 years, the female:male ratio was 2.5:1. Early, active treatment is indicated, pneumothorax is preferable. The prognosis is good since 88.8 per cent of this series recovered and were known to have been well on an average of 72.3 months after diagnosis—*Basal onset of reinfection tuberculosis*, H H Cherry, *Am J Roentgenol*, January, 1948, 59 82—(J E Farber)

**Prognosis of Minimal Tuberculosis**—The importance of being able to estimate the activity of tuberculous lesions on the roentgenogram is obvious. Recent studies by Birkelo *et al*, show that it is possible to estimate activity from the first roentgenogram in a relatively high percentage of cases. The present study was solely concerned with this prognostic factor of the roentgenologist's diagnosis in 1,100 patients followed for one month to nineteen years. Statistical examination of the data showed that there is considerable roentgenological error in prognosis but the progression rates and death rates indicate that the roentgenologist's opinion is of great value in determining the type of treatment for such cases—*The value of roentgenology in the prognosis of minimal tuberculosis*, A L Cochrane, H W Campbell & S C Stein, *Am J Roentgenol*, February, 1949, 61 155—(J E Farber)

**Minimal Tuberculosis**—A series of cases has illustrated the problems associated with the roentgenologic interpretation of minimal, pulmonary, reinfection tuberculosis. The classification of the roentgen picture on a pathological basis is not entirely satisfactory and considerable differences exist in the interpretation of the roentgenograms. Further study and correlation between necropsy and roentgenologic findings is required to establish the descriptive terminology on a more solid footing. It is hazardous to decide the prognosis or clinical significance of a lesion on the basis of one film or a few films. Pulmonary lesions may be minimal in extent and yet represent the end result of the closure of a tuberculous cavity. Round foci, linear horizontal scars, and stellate scars are examples of such lesions which may be interpreted incorrectly as minimal lesions with good prognosis. A minimal lesion can therefore best be evaluated if the whole history of the case is known. A more uniform roentgenologic interpretation of minimal tuberculosis might be possible if the National Tuberculosis classification included a statement of the total period of observation and whether the evaluation is made on the

basis of a series of films, a few films, or a single film. It would also be helpful to state, where possible, the length of time between the onset of illness and the date of the film—*Minimal tuberculosis. Problems in roentgenologic interpretation*, I. D. Bobrowitz & A. Hurst, *Radiology*, April, 1949, 52: 519—(W. J. Steininger)

**Interpretation of Roentgenograms**—From this study by experienced radiologists and from previous work, it is established that the interpretation of roentgenograms is subject to a certain degree of inherent error. If a set of similar films is read by two different observers, the likelihood is that in 16 per cent of the cases the two readers will disagree with each other as to whether or not a lesion is present. If the same person re-reads the same set of films, he is likely to disagree with himself in approximately 8 per cent of the cases. The degree of error or variation is significant but compares favorably with that found in other clinical methods and diagnostic aids. The usefulness of studies on this phenomenon may be measured by the degree to which they are aimed at understanding the reasons behind the variations and by the discovery of methods to reduce them. The results of this study indicate that among the important reasons for "missing" a positive film are the size, location, and density of a lesion, as well as the "attitude" of the observer. A technique which permits a reader to review each "preliminary" positive may reduce significantly the percentage of positive cases missed without necessitating over-reading. For mass survey work it would appear imperative (1) to select the panel of readers with great care, (2) to submit them to valid tests, and (3) whenever practicable to utilize dual reading, which is actually an economical case-finding procedure. Much work is needed on methods of describing lesions and on rational evaluation of existing classifications. It is believed that the accuracy of chest diagnostic work will be enhanced as a result of basic studies of the type outlined in this report—*On the scientific evaluation of diagnostic procedures*, L. H. Garland, *Radiology*, March, 1949, 52: 509—(W. J. Steininger)

**Tuberculous Calcification**—Calcification begins early in the development of caseating tuberculous lesions. It may be present without casting the usual roentgenographic shadow if the lesion is not packed with calcium. Of great clinical importance is the fact that a lesion which appears calcified may still be soft, caseous, and potentially dangerous—*Tuberculous calcification—A clinical and experimental study*, R. Bloch, *Am J Roentgenol*, June, 1948, 59: 853—(J. E. Farber)

#### CLINICAL STUDIES, NONTUBERCULOUS DISEASES

**Beryllium Pneumonitis**—When beryllium accidentally is introduced beneath the skin, chronic ulcers form and persist until the beryllium is removed. Surgeons have found also that beryllium alloys are unsatisfactory for repairing bony defects and lead to the formation of chronic granulation tissue. Exposure to dust and fumes containing beryllium has resulted in pulmonary disease of two clinical types: (1) an acute pneumonitis, and (2) a protracted pulmonary fibrosis with emphysema. Tissues from 7 patients who died of acute pneumonitis and from 13 who died of chronic granulomatosis induced by beryllium were studied. The pulmonary lesions in these two clinical conditions are specific and there is evidence of a transition from the acute lesions to the chronic ones. In the acute pneumonitis there is a boggy, generalized consolidation of entire lobes, simulating the stage of gray hepatization in lobar pneumonia. Microscopically, there is diffuse intraalveolar exudate composed of large mononuclear phagocytes (septal cells) and edema fluid. Intraseptal lymphocytes and plasma cells are fairly numerous also. Centriobular necrosis of the liver was seen in one case. In chronic pulmonary fibrosis or granulomatosis, the lungs are voluminous and emphysematous with many fine nodules scattered diffusely throughout them. The right ventricle of the heart is always enlarged. Microscopically there is diffuse interstitial and nodular fibrosis of the lungs with a peculiar granulom-

matous reaction. The granulomas which are typical of beryllium disease are formed, in part, within the alveolar spaces by the organization of exudate, in part, within the septal and peritruncal connective tissue. Each has a central region of fibrinoid material or granular debris and this is surrounded by a peripheral zone of fibrosis infiltrated by lymphocytes and plasma cells. The centers of the granulomas are occasionally occupied by giant cells of the Langhans' type. There are conchoidal bodies in most cases, sometimes within giant cells, sometimes lying free in debris or in fibrous tissue. The granulomas in the lungs are of the same nature as those accidentally produced in the skin and subcutaneous tissues.—*The pneumonitis and granulomatosis peculiar to beryllium workers*, F. R. Dutra, *Am J Path*, November, 1948, 24: 1187—(J. S. Woolley).

**Thoracic Complications of Amebiasis**—Hepatic abscess complicates infestations by *Endamoeba histolytica* in about 5 per cent of cases. Fifteen per cent of these develop intrathoracic complications. The ratio of male to female patients is 15:1 for unknown reasons. The age range for most is 20 to 50 years. The hepatic abscess is solitary in 65 to 88 per cent and is in the right lobe in 85 to 96 per cent since the infection usually reaches the thorax by direct extension through the diaphragm and pleura and then to the lung. If the pleural layers are adherent, the lung is invaded directly. Abscesses from the left lobe of the liver may invade the pericardium but rarely involve the left lung or pleura. Rarely, solitary pulmonary abscesses not adjacent to the diaphragm are seen, these are probably embolic in origin. In 50 per cent of cases, there is no previous history of dysentery. The most usual complaint is pain in the right lower chest and shoulder. This is followed by a cough which at first is nonproductive. Later, there is hemoptysis which is followed by expectoration of sputum which looks like chocolate or mahogany paste. There is a septic type of temperature and there are other toxic manifestations. The roentgenogram shows a characteristic hump

like localized elevation of the diaphragm, best seen in the lateral view. If there is direct extension into the lung a shadow is seen in the base of the involved lobe with its apex tapering off toward the hilus, this may contain a cavity with a fluid level. The pleural cavity may contain fluid or air and fluid, this may be general or loculated. If there is an abscess of the left lobe of the liver, roentgenogram of the stomach with barium will show it to be displaced posteriorly and laterally. The prognosis is worst if there is empyema, better if there is lung involvement alone, and best if there is a bronchohepatic fistula without pleuropulmonary involvement. The use of emetine greatly lowers the mortality; it should be used for all cases of hepatic abscess with or without pleuropulmonary complications. Surgery thus may sometimes be averted. If dysentery is present, carbarsone or diodoquine should be added. If hepatic abscesses are bulging, they should be aspirated repeatedly. Indications for surgery are (1) secondary infection, (2) empyema incurable by aspiration, (3) persistent communication between the biliary tract and bronchi and (4) fibrosis of pulmonary tissue. The liver should be drained via an extracapsular route. In empyema, thoracotomy and decortication of the lung and diaphragm should be done, the liver need not be drained. In pulmonary involvement, the damaged pulmonary tissue should be resected locally or by lobectomy. In pericardial infection, drainage should be done. Postoperatively, emetine and carbarsone or diodoquine should be given.—*Thoracic complications of amebiasis*, R. R. Shaw, *Surg, Gynec & Obst*, June, 1949, 88: 753—(A. G. Cohen).

**Friedlander's Pneumonia in Infants**—Pulmonary infection with Friedlander's bacillus (*Klebsiella pneumoniae*) is very rare in infants and few cases have been reported. The lesions apparently lack the roentgenographic signs of abscess or thin-walled cavities seen in adult. The disease may be epidemic. It fails to respond to sulfonamides and penicillin. Seven cases of atypical pneumonia are reported in infants of three weeks

to thirteen months of age. All but one had an insidious onset, all had signs of purulent bronchitis although two had normal chest roentgenograms, and each had a pure culture of *K. pneumoniae* from the throat. All failed to respond to penicillin and/or sulfadiazine but responded to the use of streptomycin — *Pneumonia in infancy caused by Friedlander's bacillus*, B F Grotts, *J Pediat*, February, 1949, 34 174 — (W H Oatway, Jr)

**Histoplasmosis in California** — The occurrence of a mild subclinical form of histoplasmosis probably is widespread. Eighty-five California children with suggestive clinical symptoms were surveyed by tuberculin and histoplasmin tests. Five patients with positive histoplasmin tests and negative tuberculin tests were found to have multiple pulmonary calcifications. Coccioidin tests were not done. Four of the five children had lived or visited in Texas, Wyoming, Arizona, or Missouri — *Histoplasmosis in California children*, Helen B Pryor, *J Pediat*, January, 1949, 34 12 — (W H Oatway, Jr)

**Erythema Nodosum** — There are three theories to explain the etiology of erythema nodosum: (1) that it is a manifestation of tuberculosis, (2) that it is a syndrome, a skin manifestation of several disease processes, (3) that erythema nodosum is an infectious disease of definite etiology, but that similar manifestations may occur "symptomatically" in other disease processes. The author's detailed histopathologic studies lead him to conclude that erythema nodosum is an independent disease of definite etiology, the causative agent of which is unknown. It is likely that certain diseases predispose the body to attack by the causative agent of erythema nodosum as they do to attack by the pneumococcus and herpes simplex virus. Apparently tuberculosis is only one of several diseases that create conditions favorable for the agent of erythema nodosum. Other predisposing causes are lymphogranuloma venereum, sarcoidosis, "atypical" pneumonia, certain streptococcal infections, and treatment with certain sul-

fonamides — *Die Aetologie des Erythema nodosum*, G Miescher, *Schweiz med Wchnschr*, March 27, 1948, 78 269 — (H Marcus)

**Linear Atelectasis** — Linear atelectasis frequently occurs in association with intra-abdominal lesions. Pathologically the atelectatic area is discoid, roentgenographically it usually appears as one or more striations. Typically these striations extend outward from the cardiac border in a horizontal or oblique direction across the lower third of one or both lung fields. Most frequently the shadows lie just above the diaphragm which is elevated and limited in motion. Linear atelectasis is always secondary to some other lesion, either intra-abdominal or intrathoracic. A total of 7,064 roentgenograms were examined, representing patients hospitalized for complaints of all types. In 29 (0.4 per cent), linear atelectasis was demonstrated. Three of the 29 cases were excluded from the series because no adequate primary source could be demonstrated. Among the remaining 26 cases, there were 22 (80 per cent) of intra-abdominal lesions and 4 (20 per cent) of thoracic lesions. The atelectasis occurred in 12 cases on the side of the involved organ, in 3 cases on the opposite side. It usually was transient but at times persisted for weeks or months. The presence of linear atelectasis, with or without a high diaphragm, affords presumptive evidence of disease within the abdomen — *The linear atelectatic sign in intra-abdominal lesions*, J L Marks & A Nathan, *Radiology*, March, 1949, 52 363 — (W J Steininger)

**Appearance of Lungs in Mitral Stenosis** — Aggregations of so-called "heart failure cells" in the lung parenchyma have been known for many years but their recognition by means of roentgenography is new and little known. The appearance simulates miliary tuberculosis. The lesions probably arise because the mitral obstruction causes increased pressure in the left auricle and ultimately in the alveolar capillaries. These become engorged and may bleed into the alveoli. Hemoglobin from the disintegrating red blood cells is converted



into soluble iron-free hematin and insoluble particles of iron-containing hemosiderin. The latter, acting as foreign bodies, are phagocytized and carried into the lymphoid tissue of the lungs, finally reaching the bronchial lymph nodes. This movement probably is slower than that in pneumoconiosis because the chronic pulmonary venous congestion obstructs the lymphatic drainage, leaving most of the hemosiderin-laden cells in the alveoli. They are radio-opaque and produce the stippling observed on the roentgenogram. Seen through a hand lens, some of the minute shadows on the roentgenogram are ring-like with the form of a rosette, the central hole being the terminal respiratory bronchiole.—*Miliary appearances in the lungs in mitral stenosis. Endogenous pulmonary hemosiderosis*, T. E. Gumpert, *Brit M J*, September 27, 1947, no 4525 488—(R. W. Clarke)

**Pulmonary Embolism**—Pulmonary embolism may occur without infarction owing to the double circulation of the lungs. The characteristic roentgenographic findings are increased radiolucency and ischemia of the involved pulmonary segment. Abrupt termination of the embolic pulmonary artery is frequently demonstrable. This contrasts strikingly with the usual area of increased density on the roentgenogram found in cases of embolism with infarction.—*Pulmonary embolism without infarction*, R. Shapiro & L. Rigler, *Am J Roentgenol*, October, 1948, 60 460—(J. L. Farber)

**Unresolved Pneumonia**—The use of this term is to be discouraged, proper study of the patient usually will reveal the correct diagnosis. Bronchiectasis, atelectasis, and intra-bronchial disease, often in association with pneumonia, are commonly responsible for so-called unresolved pneumonia. Thorough roentgenography, bronchoscopy, and bronchography may determine the underlying pathology.—*Unresolved pneumonia*, C. L. Hurd, *Am J Roentgenol*, March, 1949, 61 335—(J. E. Farber)

**Lipoid Granulomatosis**—In 1946, a 35 year-old man manifested general weakness and progressive dyspnea. Chest roentgenograms in 1938 and 1940 had revealed mottling throughout both lung fields. A film in 1946 showed extensive interstitial fibrosis throughout both lungs with moderate cardiac enlargement and prominence of the pulmonary conus. Roentgenograms disclosed a large defect in the right parietal region and cystic areas of bone destruction in both the femora and the left pubic bone. A biopsy specimen of the right parietal bone had the histopathologic picture of lipoid granuloma of the type seen in Schüller-Christian disease. Following deep roentgen-ray treatment to the chest, there was some clearing of the pulmonary infiltration. The patient, however, began to manifest cardiac decompensation which has progressed in spite of the usual therapy.—*Lipoid granulomatosis (xanthomatosis) with marked pulmonary fibrosis and cor pulmonale as outstanding manifestation*, S. J. Schneiderman & L. Schneider, *Ann Int Med*, April, 1949, 30 842—(H. R. Vayer)

**Mycotic Pulmonary Arterial Aneurysms**—A 10 year-old boy, who had no congenital defects, syphilis, or bacterial endocarditis, developed multiple pulmonary aneurysms. His illness began with a low grade thrombophlebitis of the lower extremities. This phlebitis slowly extended to the inferior vena cava and the collateral circulation developed. Small septic emboli invaded the lungs, causing thromboendarteritis of the pulmonary arteries whose walls became fibrotic, weakened, and dilated to form multiple, large, mycotic aneurysms. Roentgenograms showed several enlarging, dense patches in the peripheral area. Following a septic course with repeated hemoptyses, the patient died and autopsy findings substantiated the clinical impression.—*Thromboendarteritis and multiple mycotic aneurysms of branches of the pulmonary artery*, C. L. Pirani, F. E. Lewis, Jr., & A. L. Wilson, *Am J Dis Child*, April, 1949, 77 190—(W. H. Ogden, Jr.)

**Carcinoma of Lung**—A total of 604 patients in sixteen years were diagnosed as having primary carcinoma of the lung. The diagnosis was proved by biopsy in 481 cases, in the remainder it was established by reasonable clinical criteria. Of the patients, 85.5 per cent were men. Operation was advised unless (1) there was absolute or strong presumptive evidence that the tumor could not be resected or (2) the condition of the patient was too poor. Of the cases seen, 48 per cent were explored and resection was done in 27 per cent. In recent years, 51 per cent were explored and 32 per cent resected. The cases were divided into 3 groups: (1) no demonstrable extrapulmonary extension, (2) lymph node metastases only (gross or microscopic) and (3) gross evidence of extension. The average survival period of cases known to have died was 4.4 months for the inoperable group and 11.3 months for the group resected with no apparent extension. Among the resected cases, 24.4 per cent of those operated upon five or more years ago and 60 per cent of those operated upon one year ago or less are still alive. Of the cases resected with no apparent extension, 90.9 per cent of those operated upon during the past year were still alive, as were 33.3 per cent operated upon one to five years ago and 40 per cent of those operated upon more than five years ago. If operative deaths are excluded, the percentages rise to 100, 40, and 50, respectively. The average survival time of those dying postoperatively was 11.1 months, the longest time 28 months. If there was lymph node extension only, two-sevenths were alive more than two years later and 20 per cent were alive after five years. The average survival time of those dying was 9.6 months, the longest time 23 months. In the cases with gross extension, palliative resection was performed for many, in 24 cases, all detectable tumor tissue was removed. Only one of the 43 patients was alive after one year. The average duration of life was 10 months and the longest survival period was 29 months. The procedure of choice was pneumonectomy, except in 8 aged persons with a localized tumor, for whom lobectomy was performed. Four survived

more than two years but all are dead, 4 operated less than two years ago are all living. The pathological types were (1) undifferentiated, (2) carcinoma arising from glandular epithelium and (3) epidermoid. The following statistics pertain only to those patients who survived the operation. In the group with undifferentiated carcinoma, none was living after three years. The average duration of life was 9.3 months and the longest survival 29 months. In the adenocarcinoma group, one of 6 is alive after three years, the average duration of life was 10.2 months. In the carcinoma simplex group, none is alive after one year, the average duration of life was 7.3 months. In the epidermoid group the results were grade I, 40 per cent alive after two years, 37.5 after three years, 40 per cent after ten years, with an average survival time of 15.1 months and a maximum of 27 months; grade II, 44.4 per cent alive after three years, 50 per cent after five years, with average survival time of 12.9 months and a maximum of 24 months; grade III, 50 per cent alive after five years, with an average survival time of 8.4 months and a maximum of 28 months. Altogether 10 patients are living after five years. No patient who lived for 30 months later died of the disease.—*Survival in primary carcinoma of the lung*, R. H. Overholt & I. C. Schmidt, *New England J. Med.*, March 31, 1949, 240:491.—(A. G. Cohen)

**Cytologic Diagnosis of Lung Cancer**—From 671 cases of suspected lung cancer or undiagnosed chest disease, 2,228 sputum specimens or bronchial aspirates were submitted to cytologic examination. Of these 671 cases, 100 proved to be carcinoma of the lung. Sputum from 89 of the 100 proved cases was examined and cells "consistent with malignancy" or "suspicious" were found in 63 (71 per cent). Secretions obtained bronchoscopically from 45 proved cases were studied and positive findings were reported in 26 (58 per cent). It was found necessary to examine at least 3 slides from each of 5 daily sputum specimens before the cytologic examination could be considered adequate.

When these complete studies were made, the accuracy of cytologic diagnosis was increased to 90 per cent (63 of 69 proved cases). On the other hand, the number of specimens examined was inadequate in 20 of the 26 proved cases missed by sputum examination, in 12 cases a single specimen was submitted. When sputum and bronchial aspirates from the same cases were examined, the results were comparable. The relative ease with which sputum smears may be prepared makes this diagnostic procedure available where adequate diagnostic facilities, such as bronchoscopy, are lacking. However, the technique of cytologic examination has definite limitations and further evaluation under rigid investigative control is necessary before it can take its proper place in the diagnosis of bronchogenic carcinoma.—*Diagnosis of bronchogenic carcinoma by cytologic methods*, S M Farber, M A Benioff & A K McGrath, Jr., *Radiology*, April, 1949, 52: 511—(W J Steininger)

**Aspiration Biopsy of Lung Lesions**—During the years 1936 through 1947, the authors performed needle biopsies on 272 lesions of the lung, in 231 patients. Of these patients, 220 were suspected of having bronchogenic carcinoma not accessible to bronchoscopy. In 11 patients, the biopsy was done for other suspected intrathoracic lesions but lung tissue was traversed. Of the 220 patients, 163 were proved to have carcinoma of the lung by a definite pathologic report on material obtained by needle biopsy, by subsequent bronchoscopic biopsy, or by exploratory thoracotomy which was used as the final resort, 135 were proved to have pulmonary carcinoma by needle biopsy. The positive diagnosis rate was, therefore, approximately 61 per cent. There was one false positive result. The method lent itself especially well to soft carcinomas located peripherally in the lung. There was little success in diagnosing firm, solid, benign lesions or lymphoblastomas. The procedure is simple but not without hazard and should be used only when a definite diagnosis of

carcinoma cannot be made by bronchoscopy or sputum analysis. Complications developed following 20 (7.3 per cent) of the needle biopsies. Three patients died shortly after the procedure: one from tension pneumothorax, one from shock and convulsions, and the third from coronary thrombosis. There were only two serious pneumothoraces, both in patients with marked emphysema which makes the procedure hazardous. One patient developed a central facial palsy within seven days and died later of metastatic tumor. No case of empyema developed and there was no evidence of the spread of tumor along the needle track. The method is relatively useless unless a biplane or multiplane fluoroscope and a competent fluoroscopist are available. The pathologist must be willing to make a diagnosis from a very small specimen.—*Value and limitations of aspiration biopsy for lung lesions*, G P Rosemond, W E Burrell & J H Hall, *Radiology*, April, 1949, 52: 506—(W J Steininger)

**Dysgerminoma**—Invasion of pulmonary tissue by dysgerminoma has been demonstrated only rarely in the living patient. A 48-year-old white woman survived seven and one half years after removal of a dysgerminoma followed by deep roentgen irradiation and male sex hormone therapy. A pulmonary lesion was first noted on a chest roentgenogram taken two and three quarter years after operation for the primary tumor. The progress and growth of this lesion was followed for four years. Good palliation was obtained from the administration of testosterone propionate over a two year period during which time the pulmonary metastasis slowly grew larger. Later, mediastinal involvement was demonstrated with invasion of the opposite lung. The lung metastases regressed less than 50 per cent following a series of deep roentgen treatments. Other metastases occurred in the supraclavicular, inguinal, abdominal, mediastinal, and retroperitoneal lymph glands, the kidneys, and the liver.—*Dysgerminoma of Ovary with pulmonary metastases, results of treatment and survival*

and male sex hormone, *P E Russo & J W Kelso, Radiology, March, 1949, 52 567—(W J Steininger)*

**Massive Pleural Tumor**—Primary tumors of the pleura, either diffuse or localized, are the least common intrathoracic tumors. The diffuse tumor is the mesothelioma which is malignant and not resectable. Localized tumors arise from the subpleural connective tissue layers. Those on the parietal side often show a tendency toward infiltrative growth and metastases. Tumors arising from the visceral pleural surface include the sarcomas which may be pedunculated and show little tendency to infiltrate or to metastasize although they are considered sarcomatous. They are easily removed and cause death only because of the gigantic size to which they may grow. When small, such circumscribed tumors are diagnosed with difficulty, if at all, without exploration. Aspiration biopsy may aid. Bronchoscopy shows no lesion. A lobulated fibrosarcoma weighing 3,230 Gm was successfully removed from a 52-year-old woman. Over two years she had gradually developed increasing dyspnea on exertion which culminated in severe orthopnea with congestive failure. A chest film taken ten years previously showed a lobulated density in the right lower lung field. Serial chest films showed gradual progressive enlargement of this density and at operation the encapsulated tumor nearly filled the entire hemithorax. The signs and symptoms of congestive failure due to mechanical encroachment upon the left auricle disappeared promptly after the tumor was removed. Follow-up examination nearly three years after removal showed the patient to be well and asymptomatic with no evidence of local recurrence of the neoplasm.—*Fibrosarcoma of the pleura mechanically causing congestive cardiac failure. Successful surgical removal, I A Sarot, Quart Bull, Sea View Hosp, July, 1948, 10 109—(K T Bird)*

**Hamartoma of Lung**—Hamartomas of the lung are tumor-like masses containing

some or all of the normal histological elements which make up mature bronchi or lung tissue, quantitatively grouped in abnormal proportions so that one tissue element, usually cartilage, predominates. The tendency of hamartomas of the lung to undergo calcification or ossification is important from the roentgenological point of view. Large hamartomas which contain calcium or bone can be diagnosed with reasonable accuracy from roentgenograms alone. Small lesions which are of more common occurrence are more likely to simulate metastatic nodules or primary bronchogenic carcinomas and they cannot be diagnosed specifically from the roentgenograms. (Author's Summary)—*Roentgenologic significance of hamartoma of the lung, W C Hall, Am J Roentgenol, November, 1948, 60 605—(J E Farber)*

**Gangrene from Grass**—Aspiration of timothy grass into the tracheobronchial tree is common. The grass is progressively propelled into the lung periphery, severe and prolonged complications may follow, including lung abscess, suppuration, bronchiectasis and, rarely, gangrene. A case is presented in which, for the first time, gangrene is reported as a sequel. An infant of 21 months swallowed some timothy hay, developed pulmonary suppuration, failed to respond to bronchoscopy and surgical drainage, and died 37 days after the onset. Autopsy demonstrated a diffuse purulent bronchitis, lung abscess of the right lower and middle lobes, and gangrene of the upper lobe.—*Pulmonary gangrene of a child following aspiration of timothy grass, D J Judge, E C Rice, & E W Davis, J Pediatr, January, 1949, 34 87—(W H Oatway, Jr)*

**Obstruction of Superior Vena Cava**—Of 250 cases of superior vena caval obstruction reported from 1904 to 1946, 145 were proved by autopsy or operation, the remainder were diagnosed on good clinical evidence. The thin-walled superior vena cava is easily compressible. Its close proximity to the aorta and tracheobronchial structures makes it

highly vulnerable to an extension of inflammatory or neoplastic processes from these areas. The right anterior mediastinal and right laterotracheal chains of lymph nodes are also intimately associated with this vein. Increased collateral circulation is an important consequence of caval obstruction and involves chiefly the internal mammary, vertebral, azygos, and lateral thoracic veins. Of 166 patients whose sex is reported, 79.5 per cent were men. The highest incidence is between the ages of 30 and 60 years. The three most common causes were malignant primary thoracic tumors (29.6 per cent), aortic aneurysms (24.0 per cent), and chronic fibrous mediastinitis (24.8 per cent). The latter includes tuberculosis, syphilis, and a group of diseases whose cause is unknown. From 1904 to 1946 the incidence of syphilitic mediastinitis in this series dropped from 28.6 to 0.9 per cent. In the nonspecific group of chronic fibrous mediastinitis it is probable that a trauma or respiratory infection leading to inflammation of the tracheobronchial lymph nodes plays a role. Since 1904, 19 cases of localized phlebitis with thrombus formation have been reported. The chief clinical manifestations of superior caval obstruction are evidence of the increased venous pressure in the regions drained by this vein and include edema of upper extremities, head and neck, cyanosis, dyspnea, headache, and chest pain. Hoarseness, dysphagia, and convulsions may be present. Diodrast visualization is valuable in revealing the site of obstruction but is rarely needed to make the diagnosis. Treatment is directed at the underlying disease. In chronic mediastinitis, mediastinotomy with release of any constrictive bands is indicated. Repeated phlebotomies may afford symptomatic relief. The prognosis varies with the underlying disease and some patients with good collateral circulation have survived for many years.—*Obstruction of the superior vena cava. A review of the literature and report of two personal cases, F. T. McIntire & E. M. Sykes, Jr., Ann Int Med, May, 1949, 39: 925—(H. R. Nayer)*

**Traumatic Bronchial Rupture**—Severe chest injuries may cause tears in the main stem bronchi at or close to the bifurcation of the trachea. When this occurs, the patient usually reveals shock, dyspnea, anoxia, interstitial emphysema, and cough. Whereas such accidents may cause death, patients have survived the immediate effects of their injury to develop posttraumatic bronchial occlusion with pulmonary collapse. Routine roentgenograms of the chest immediately after injury may reveal fractured ribs, interstitial emphysema, pneumothorax, pulmonary compression, and mediastinal shift. Later, when bronchial occlusion is complete, the classical roentgen manifestations of pulmonary collapse develop. Bronchograms reveal a cup-shaped blind pouch at the site of the occlusion. Substernal distress and dyspnea occur commonly in patients with posttraumatic bronchial occlusion. (Authors' summary)—*Traumatic bronchial rupture with occlusion, P. J. Hodes, J. Johnson & J. P. Atkins, Am J Roentgenol, October, 1948, 60: 448—(J. E. Farber)*

**Angiocardiography of Great Vessels**—Conventional roentgen measurement of the great vessels is indirect, often inaccurate, and not well standardized. Angiocardiographic measurement of the great vessels is simple, accurate, and capable of standardization. The caliber of the ascending aortic arch gradually increases with age. It averaged in this series 28.6 mm and ranged from 16 mm to an upper limit of 38 mm. A simple and satisfactory evaluation of the pulmonary artery may be found in measurement of the right pulmonary artery in the frontal projection. In this series it averaged 23.4 mm and ranged from 17 to an upper limit of 30 mm. It is anticipated that larger series of angiocardiographic measurements will supplement this preliminary report. (Authors' Summary)—*The angiocardiographic measurement of the normal great vessels, C. T. Dotter & I. Steinberg, Radiology, March, 1949, 52: 553—(W. J. Steininger)*

## ANTIMICROBIAL THERAPY

**Streptomycin in Tuberculous Enteritis**—Thirty-three cases of tuberculous enteritis were treated with streptomycin in a cooperative study involving 15 Veterans Administration hospitals. Intestinal symptoms had been present for an average of five months before streptomycin therapy. The mean known duration of the coexisting pulmonary disease was nineteen months. The daily intramuscular streptomycin dose varied between 10 and 20 Gm, at the present time 10 Gm is recommended in 2 doses. Nineteen patients completed courses of 60 to 120 days. Fourteen-day courses were used in 6 cases for symptomatic relief only. Eight cases are still under treatment. Oral treatment, 2 Gm daily in 5 doses, was used in 2 patients for 66 and 120 days and in 3 patients for seven to fourteen days. Intramuscular streptomycin was uniformly effective in the relief of symptoms of tuberculous enteritis. Maximum subjective benefit was reached within one week in the majority of cases. Relief of diffused and localized tenderness, rigidity, and distention followed within a few days. With oral streptomycin four to six weeks of treatment were required for complete relief of symptoms. Intestinal symptoms recurred in 2 out of the 33 cases. A larger series and a longer follow-up will be necessary before the rate of remission can be established. Of the patients whose treatment had been completed, the average follow-up was six and one-half months. The roentgen-ray reports were summarized in 17 cases. All showed abnormalities before treatment. In 6 of this group the findings returned to normal after treatment. In 8 cases definite improvement was seen but some residual deformity remained. Two cases showed marked residual abnormality and one case developed signs of small bowel obstruction. A return to radiologic normalcy can be expected provided the abnormalities are primarily those of local irritation (i.e. spasm, hypermotility, loss of haustrations, mucosal irregularity, and others). Where ulceration has been deeper, more widespread, and of

longer duration, and where lymphatic obstruction and interstitial inflammation have destroyed normal architecture of the bowel wall, radiologic changes may persist and there may be further distortion due to cicatricial contraction—*Streptomycin in the treatment of tuberculous enteritis, a report of thirty-three cases, E F Mason, W W Kridelbaugh, W H Crouch & M Ward, Am J M Sc, January, 1949, 217-28*—(W J Steininger)

**Streptomycin and Clotting Time**—The effect of streptomycin on the blood clotting and prothrombin times of 21 patients with pulmonary tuberculosis was studied by modifications of the Lee-White and Quiek techniques. A closely parallel series of 21 phthisic patients served as a control. Each patient in the streptomycin group received 0.5 Gm of streptomycin twice daily for 120 days. No correlation between the age, activity or extent of the tuberculosis and the clotting or prothrombin times was found in either the control or streptomycin groups. Two methods of investigation were used: (1) tests were made during the same hours on different days over a period of several weeks, (2) serial tests were performed prior to and at 15, 30, and 90 minutes following the injection of streptomycin or of distilled water. No significant effect upon the prothrombin time could be demonstrated by either method but the data suggests that streptomycin exerts an anticoagulant effect particularly at 90 minutes after injection. There is no evidence that the tuberculous process itself affects the behavior of the clotting and prothrombin times in response to streptomycin but this possibility was not excluded—*Effect of streptomycin on blood-clotting time and prothrombin-time in man, L Elson, Am J M Sc, April, 1949, 217-421*—(W J Steininger)

**Para-aminosalicylic Acid for Tuberculosis**—Ten patients with pulmonary tuberculosis were treated with para-aminosalicylic acid for periods of three months. They were all

young individuals with extensive bilateral progressive disease with toxic manifestations of the disease. At first the daily dosage was 5 Gm every six hours. Later a weekly schedule was arranged of 30 Gm daily for the first two days, 20 Gm daily for the next four days, and no drug on the seventh day. All patients developed gastro-intestinal symptoms which varied in severity with the dosage of the drug. One patient developed a rash. In almost one-half of the cases, there was some clinical improvement but in no case was there complete clearing. Some patients had only a decrease in toxemia.—*Para-aminosalicylic acid*, E A Joules & E Nassau, *Tubercle*, May, 1949, 30: 98.—(A G Cohen)

**PAS for Bronchial and Urinary Tuberculosis**—The authors treated tuberculous tracheobronchitis and genito-urinary tuberculosis with para-aminosalicylic acid (PAS). Five patients who had extensive tracheobronchitis with ulceration and hyperplasia received a total dosage of 97 to 722 Gm. The daily dosage was between 12 and 15 Gm given continuously or in interrupted courses of four days each. Symptoms decreased after treatment for seven to ten days and bronchoscopic improvement was observed after two to three weeks. In patients who had had previous streptomycin treatment with residual stenosis, a good result was achieved with PAS and dilatation. Tuberculosis of the genito-urinary tract was treated in 12 patients. The results were good in disease of the lower tract, tuberculous cystitis responding most readily. The kidney lesions were not influenced. One month of treatment was sufficient to allay the distressing dysuria and frequency in 9 of the 12 cases. Encouraging results were seen in certain cases of pulmonary tuberculosis, 20 of 40 patients with progressive lesions were markedly improved. Of these 20 patients, 15 had permanent loss of bacilli from the sputum. In 5 cases of pleurisy with effusion, no effect of PAS was demonstrable. In tuberculous meningitis a combination of streptomycin and PAS treatment was used with good

results. In these cases PAS was given by a continuous duodenal drip of a 5 per cent solution in saline. It is felt that treatment with streptomycin and PAS simultaneously may give better results in the treatment of tuberculosis than when either drug is given alone.—*Die Therapie der Tuberkulose mit PAS (Paraaminosalicylsäure) mit besonderer Berücksichtigung der Bronchial und Nierentuberkulose*, R Hug, S Moeschlin & E Tanner, *Schweiz med Wchnschr*, April 23, 1949, 79: 553.—(H Marcus)

**Infection after Pulmonary Resection**—From 1942 to 1947, 427 patients were subjected to pneumonectomy or lobectomy at the Massachusetts General Hospital. Sulphonamide drugs were used throughout this period and penicillin was introduced in 1944. During this interval, the use of tourniquet ligation of the hilar strictures was replaced more and more by individual ligation. Another technical advance was the careful suture of the bronchus and the capping of the closed stump with a pleural flap. Resection was performed for many diseases, particularly bronchiectasis, abscess, tuberculosis, and carcinoma. In six years, the gross mortality for pneumonectomy fell from 21.4 to 8.3 per cent and for lobectomy from 8.7 to 2.9 per cent. In 1947, there were no deaths from sepsis. In the first five years the empyema rate dropped from 21.4 to 3.7 per cent for pneumonectomy and from 27.7 to 2.0 per cent for lobectomy. In 1947, the rates were 2.17 and 1.5 per cent respectively. In 1944, one-half of the patients who died had empyema. Thereafter, this incidence gradually declined to zero. In cases of bronchiectasis, the patients are treated preoperatively with aerosol penicillin to which streptomycin sometimes is added. If empyema develops, daily aspiration and instillation of penicillin is often helpful; penicillin has hastened the cure of bronchopleural fistulae. Sulphonamide drugs reduced the empyema rate and penicillin did even better, but a combination of both is best. Each year, the length of hospital stay has gradually shortened. The preopera-

tive routine now is to give 100,000 units of penicillin every eight hours and 0.25 Gm of streptomycin four times a day for two days. If fever is present, these may be given longer. If there is copious expectoration, 50,000 units of penicillin in one cc of saline are given as aerosol four times a day, streptomycin may be added. Before closing the chest, 100,000 units of penicillin and 1.0 Gm of streptomycin dissolved in 30 cc of saline are left in the pleural cavity. The injection of both drugs is continued for five to six days.—*The occurrence of infection after pulmonary resection*, C C Miller & R H Sweet, *New England J Med*, April 14, 1949, 240:559—(A G Cohen)

#### LABORATORY STUDIES

**Dubos Medium for Streptomycin Sensitivity Tests**—Tubercle bacilli were isolated from 140 tuberculous patients prior to treatment with streptomycin using egg slants and a Dubos albumin-Tween medium, the latter containing 10 units of penicillin per ml. Subcultures then were grown in tubes of Dubos medium containing various amounts of streptomycin. Cultures that grew on the Dubos penicillin medium were planted directly into the tubes containing streptomycin. The egg cultures had to be subcultured in a Dubos broth before being used for the sensitivity tests. Of the 140 cultures 138 were sensitive to one unit or less of streptomycin, one to 2 units and one to 3 units. It is concluded that this Dubos medium is satisfactory for testing the streptomycin sensitivity of tubercle bacilli and that most strains isolated before treatment are highly sensitive to the drug.—*Value of Dubos medium in tests for streptomycin sensitivity of Mycobacterium tuberculosis*, M Mollov & A Oshinsky, *Am J Clin Path*, January 1949, 19:67—(J S Woolley)

**Kinetics of Benzoic Acid Oxidation**—The kinetics of the oxidation of benzoic acid by *Mycobacterium tuberculosis* BCG S240 were analyzed. Six consecutive monomolecular reactions were postulated and the

velocity constants given. Oxidation began with a latent period during which adaptive enzymes were formed. This latent period became shorter or vanished if the bacteria were treated previously with small amounts of benzoic acid. Enzymes gradually disappeared in the absence of benzoic acid. The effect of streptomycin was to depress equally all stages of oxidation. *The kinetics of the oxidation of benzoic acid by certain mycobacteria*, G S Ladic, F Bernheim, & R J Fitzgerald, *J Biol Chem*, November, 1948, 176:557—(F B Sibert)

**Bronchial Arteries in Bronchiectasis**—In the normal lung, anastomoses may occur between the two arterial systems but interarterial communications are more common in the presence of disease. A study of the bronchial arteries by Wood and Miller showed that frequent enlargement of these arteries and numerous large anastomoses with the pulmonary artery were present in subjects with tuberculosis. They also occurred in association with chronic passive congestion, Ayerza's disease, silicosis, emphysema, asthma, and "congenital cystic disease" of the lung. One instance in a case of bronchiectasis was mentioned. In the present study observations are reported on 18 specimens of lung removed surgically from patients with bronchiectasis and prepared as colored casts by the vinylite corrosion technique. In 15 of these specimens great enlargement of the bronchial arteries and numerous anastomoses of these vessels with the pulmonary arteries were observed. The communications were multiple and usually occurred in the walls of the bronchiectatic sacs of the fourth order or more distal branches of the segmental bronchi. In half of the specimens the anastomoses were 1.0 mm or more in diameter. The enlargement of the bronchial vessels was associated with the development of granulation tissue during the pneumonitis that usually precedes bronchiectasis and with the increased metabolism of hypertrophied muscle and hyperplastic lymphoid tissue. The anastomoses may represent per-



sistent communicating channels originating in the granulation tissue which received vessels from both the bronchial and pulmonary arterial systems. The anastomoses are so large and numerous as to suggest that they have physiologic importance (1) in shunting pulmonary arterial blood away from the diseased tissue into relatively intact parenchyma where the pulmonary blood pressure is presumably lower, and (2) in producing hypertension in the pulmonary circulation—*Enlargement of the bronchial arteries, and their anastomoses with the pulmonary arteries in bronchiectasis*, A A Luebow, M R Hales & G E Lindslog, *Am J Path*, March, 1949, 25 211—(J S Woolley)

**Oil Pneumonia**—A controversy in the literature has occurred as the result of different observations on the effect of aspiration of peanut kernels, peanut extracts, and other peanut products. It has been shown that simple, neutral vegetable oils such as iodized sesame, poppyseed, and olive oils produce no reaction or injury to the lungs. In the present experiments peanut oil was introduced into the bronchial tree of rabbits. Lipid pneumonia was produced but it cleared in ten days leaving oil-containing macrophages. The phagocytes remained for ten weeks or more although no harm to the lung structure occurred. These results demonstrate the lack of a marked toxicity of peanut oil—*Experimental peanut oil pneumonia in rabbits*, W G Gobbel Jr, *Am J Dis Child*, February, 1949, 77 175—(W H Oatway Jr)

**Fluorescent Microscopy of Tubercle Bacilli**—Fluorescent microscopy, using the auramine stain for the detection of acid-fast bacilli, has not replaced the Ziehl-Neelsen technique as confidently predicted. Letters were addressed to the directors of 48 state health department laboratories and 39 replies were received. These replies revealed that only 24 laboratories had experimented with this method and in only 2 of these was it now

being used routinely as superior to the conventional Ziehl-Neelsen technique. The present paper discusses the application of the method to sputum examination. If the lighting and staining (auramine) are satisfactory, thin smears from untreated specimens of sputum give optimum results, including good fluorescence, little interference, and few atypical bacilli or artefacts. A dark room is essential to reduce interfering outside light and minimize fatigue. The bacilli may be injured by mechanical handling of sputum and by chemicals or heat. Such injury introduces interfering fluorescence which tends to reduce or blur the sharp brilliance of the bacilli and to induce fatigue of the worker. This fatigue was the main reason given by the laboratory directors for discarding the method. Pencil introduces no undesirable effects and appears to be satisfactory as a storage or shipping medium for sputum. Cresol and Lysol, however, are unsatisfactory as shipping mediums, Cresol because it introduces interfering fluorescence, Lysol because of apparent dissolution of the bacillus, and alteration in morphology. Centrifugation increases the number of interfering fluorescent particles more than any other single factor tested—*Limitations of fluorescent microscopy for detection of acid-fast bacilli*, H E Land, *Am J Clin Path*, January 1949, 19 72—(J S Woolley)

#### PUBLIC HEALTH AND EPIDEMIOLOGY

**Overcrowding and Tuberculous Mortality**—Although the mortality from tuberculosis in the Netherlands is among the lowest in the world and is still falling, there is an alarming increase in the number of active cases reported in that country. The great post-war shortage of sanitarium beds has made it necessary to treat many infectious cases at home, but the severe housing shortage has increased the public health risk from each case so treated. Nearly 150,000 persons have no living quarters in regular dwellings. In

1947 the average number of persons per room was 4.5 in some regions, the national average was 0.9 per room. During the latter part of 1948, visits were made to 819 homes of tuberculous patients in five cities of various sizes to study the housing of such persons. Of the patients, 299 (37 per cent) were infectious and there were children under 16 years of age in 140 of the families of such patients. There was no separate room for 99 of the infectious persons and 72 did not have even a separate bed, 79 of the families lived "doubled up" with other families. A similar survey in Amsterdam during April, 1949, revealed that in 1,933 families, there were 2,046 patients with tubercle bacilli in the sputum and 351 persons with active tuberculosis but without detectable bacilli. These families included 6,091 adults and 1,667 children under the age of 15. Of the 2,046 infectious patients, 771 slept in separate beds but with other persons in the same room, 93 with children under 15 in the room. Another 303 patients slept with other persons in the same bed, another 126 slept in the family's living room. Of the 1,933 families, 269 lived "doubled up." The solution obviously must be the creation of more housing units and more sanitarium beds.—*Onderzoek naar de woningtoestanden van thuis verpleegde tuberculose-patiënten, die onder toezicht staan van de consultatiebureau's te Eindhoven, Den Haag, Maastricht, Nijmegen en Venray, A. E. G. de Vries Bruins, Tegen de Tuberculose, May-June, 1949, 45-60*—(J. van der Vaele)

**BCG for Students**—At the Cook County Hospital in Chicago 142 nursing students have been vaccinated with BCG since 1940, each had a normal chest roentgenogram and a negative reaction to 1 mg. of OT during her first week of training. None of this group has developed tuberculosis although they were allowed to work in the tuberculosis unit. A control group of 199 nonreactors who were not vaccinated was not allowed to have contact with known tuberculous patients but 3 of the group developed the disease. Three

other cases developed during the same period among 286 nurses who reacted positively to tuberculin at the start of training. In a group of 109 medical students who were vaccinated at the University of Illinois since 1939, no case of tuberculosis has developed, 4 cases developed in the nonvaccinated group.—*BCG vaccination among medical and nursing students, E. E. Irons, Am J Dis Child, March, 1949, 77-376*—(W. H. Oatway Jr.)

**BCG Usage in Chicago**—The continuous study of BCG for 13 years in Chicago represents the longest project of its kind in the United States. It has shown BCG to be safe. From a group of newborn infants in a heavily infected environment, 1,417 were vaccinated and 1,414 were used as controls over a ten-year period. Chest roentgenograms of the vaccinated group showed that 11 developed tuberculous lesions, and one child died, 39 lesions appeared in the nonvaccinated group and 7 deaths occurred. In a second group of infants from tuberculous households vaccinated and control infants were isolated in foster homes. Two lesions and no deaths occurred in the 151 vaccinated children, 5 lesions and 4 deaths occurred in the 105 controls. A third group was made up of children under 10 years of age, all living in a single housing project. Of these children 699 were vaccinated during a 5-year period, no case of tuberculosis developed. In 625 non-reacting alternately selected controls, there were 4 cases of the disease. Among 275 positive reactors in this third group, 2 lesions and one death occurred. It is suggested that only the portions of the population most likely to be infected be vaccinated. The most efficient approach is through schools and nurseries.—*BCG vaccination in Chicago, R. A. Black, Am J Dis Child, March, 1949, 77-381*—(W. H. Oatway Jr.)

**Mass Surveys**—Approximately 500,000 persons in Washington, D. C., were examined in a chest roentgenogram survey during 1948. Of this number, one per cent was found to

have definite tuberculosis and another 14 per cent had suspected tuberculosis. In addition, 14 per cent were thought to have cardiac or other abnormalities. More than 5,000 of the cases of definite tuberculosis were new, 83 to 85 per cent were minimal—*Some medical and roentgenological aspects of mass chest surveys, A. C. Christie, Am J Roentgenol, February, 1949, 61: 147*—(J. E. Farber)

**Tuberculosis Among Students**—A continuous program of tuberculosis control has been conducted at the University of Pennsylvania where the average annual enrollment has been about 6,000. During the past fifteen years, 177 students were found to have pulmonary tuberculosis. In 1931, 48 per cent of the entering students were tuberculin-positive, in 1946 only 28 per cent were reactors in spite of the fact that the average age of the latter group was considerably higher. Of the 177 tuberculous students, 91 were medical students who comprised only 9 per cent of the total enrollment. The non-medical students had an attack rate of 5.7 per 1,000. All tuberculous students were removed from school and readmitted only after the lesion was stabilized. Only 6 of the nonmedical students failed to be readmitted.

The medical students had an attack rate of 39.6 per 1,000. Ten students entered medical school with lesions, 81 developed the disease during their course. There were also 5 students who developed serofibrinous pleurisy and were granted a year's leave of absence. Seniors accounted for 38.6 per cent of the new cases, juniors 49.1 per cent, and the sophomores 12.3 per cent. Most of the new lesions detected in the third year were found in the first few weeks of the school and there was a high rate of conversion from negative to positive tuberculin reactors during the second year. The teaching of physical diagnosis and pathology now has been modified to reduce contact with tuberculous patients and autopsy specimens. Among the medical students, the appearance of a parenchymal lesion of the reinfection type rarely followed closely upon a primary infection, this interval was less than a year in only one instance. Reinfection type lesions appeared more often in students who entered as tuberculin reactors than in those who entered as non-reactors. Four students developed lesions of the primary type, these appeared 6 to 8 months after the development of sensitivity to tuberculin—*Tuberculosis among medical and academic students, H. D. Lees, Dis of Chest, May, 1949, 15: 569*—(E. A. Rouff)

# VARIATION IN THE DURATION OF TUBERCULIN SKIN SENSITIVITY PRODUCED BY TWO STRAINS OF BCG<sup>1 2</sup>

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## INTRODUCTION

It is probable that the revived interest in the use of BCG vaccine as an auxiliary means for preventing tuberculosis will result in its more extensive employment. Any variable which might influence its success should be adequately controlled.

A recent experience of the writers with the administration of BCG to a group of nurses and medical students has brought to light a significant variable which is believed to be important. A BCG vaccine prepared in one laboratory was capable of causing a high percentage of tuberculin reactors, followed by a rapid loss of skin sensitivity to tuberculin. Another vaccine prepared in a different laboratory produced a prompt and sustained reactivity to tuberculin. These divergent results are thought to be related principally to some fundamental difference in the vaccines employed in this study. Moreover, it is felt that standardized methods of vaccine preparation and administration should be worked out before any extensive program of vaccination is planned.

## METHODS AND RESULTS

In this study, two groups of individuals were vaccinated with BCG (*Bacillus Calmette-Guérin*) vaccine obtained from two different sources. Group A consisted of 103 nurses and medical students with an age distribution of 18 to 26 years. These individuals were vaccinated in September 1946 with a strain of BCG (Vaccine A) originally obtained from the Pasteur Institute and maintained in this country for several years. Vaccine A was made by a worker with long experience in preparation and use of BCG. It contained 15 mg. of bacteria in each ml., was shipped in refrigerated container, and arrived two days after preparation (twelve hours after leaving the laboratory of origin). Upon arrival it was immediately placed under refrigeration. Vaccination was then carried out twenty-four to forty-eight hours later by the percutaneous method described by Rosenthal (17).

All individuals were examined two weeks after vaccination and, with few exceptions, were noted to have developed a characteristic papular eruption at the site of inoculation. Tuberculin tests were performed at one-, three-, six-, nine-, and twelve-month intervals from the time of vaccination. The results of these tests are recorded in table 1.

<sup>1</sup> From the Department of Medicine of the University of Rochester School of Medicine and Dentistry, and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals, Rochester, New York.

<sup>2</sup> Funds for this investigation came from the Helen W. Rivas Fund of the University of Rochester School of Medicine and Dentistry.

One month after vaccination, a well-developed skin sensitivity (2 or 3 plus)\* to 0.005 mg of PPD was observed in 88.3 per cent of the vaccinated individuals.

Three months after vaccination, 79.2 per cent reacted to 0.005 mg of PPD. In addition, a decreased intensity of skin reaction was observed. Most of the vaccinated individuals had declined from a 2 or 3 plus reaction to one plus or a questionable reaction. In order to exclude decreased potency in the testing material as a cause for the decreased tuberculin reactions, 0.005 mg of PPD and 1.0 mg of O.T. were compared by injecting each substance into different sites on the same forearm. A more intense tuberculin reaction resulted when 1.0 mg of O.T. was used. In all subsequent tuberculin tests, only O.T. (0.1 mg followed by 1.0 mg if 0.1 mg gave a negative reaction) was employed for determining tuberculin sensitivity.

TABLE 1  
*Results of Vaccination with Vaccine A*  
*Vaccinated September 1946 (108 Individuals)*

MONTHS AFTER VACCINATION	NUMBER TESTED	NUMBER POSITIVE TO TUBERCULIN	PER CENT POSITIVE	NUMBER OF DOUBTFUL REACTIONS
1	103	91	88.3	9
3	101	80	79.2	9
6	98	38	38.7	18
9	69*	8	11.6	6
12	102	11	10.7	8

\* One group of nurses comprising 33 individuals not tested at the nine-month interval.

Six months after vaccination, 38.8 per cent of the vaccinated individuals had a positive reaction to 1.0 mg of O.T. The potency of tuberculin was again tested by comparing three different commercial tuberculins for ability to produce a positive skin reaction. No variation was detected, which seems to exclude the tuberculin as a factor responsible for the marked reduction in positive reactors.

The progressive decline in tuberculin skin sensitivity continued and nine months after vaccination only 11.6 per cent of Group A were positive reactors. Twelve months after vaccination, only 10.7 per cent had a positive tuberculin reaction to 1.0 mg O.T. If those who had doubtful reactions are included, only 18.6 per cent demonstrated a positive tuberculin reaction one year after administration of Vaccine A.

Group B consisted of 178 medical students and nurses with the same age distribution as Group A. Of these, 100 had never received BCG vaccination. Seventy-eight of this group had been vaccinated in September 1946 with Vaccine A. They had previously developed a positive tuberculin reaction as a result of vaccination but had reverted to a negative reaction by the end of a year or less. All individuals in Group B were vaccinated in September 1947 with a vaccine prepared in another recognized laboratory. Vaccine B was made under carefully

\* Tuberculin tests were classified according to criteria established in the 1940 edition of *Diagnostic Standards of Tuberculosis* of the National Tuberculosis Association.

controlled conditions and under the supervision of an individual who has had long experience in BCG preparation and use. This vaccine, containing 20 mg of bacteria per cc, reached us (unrefrigerated) twenty-four to thirty-six hours after shipment. It was immediately placed under refrigeration and used twenty-four to ninety-six hours later. Vaccine B was administered in exactly the same manner as Vaccine A. Similarly, all individuals were observed two weeks after vaccination and were found to have developed a characteristic papular reaction at the vaccination site.

It was observed, however, that Vaccine B produced a more intense and prolonged local reaction than Vaccine A. Several individuals developed small, suppurating lesions at the vaccination site which persisted for several months. The increased local reaction occurred with the same frequency in the individuals vaccinated for the first time as in those revaccinated one year after a previous

TABLE 2  
*Results of Vaccination with Vaccine B*  
*Vaccinated September 1947 (178 Individuals)*

	MONTHS AFTER VACCINA TION	NUMBER TESTED	NUMBER POSITIVE TO TUBERCULIN	PER CENT POSITIVE	NUMBER OF DOUBTFUL REACTIONS
Vaccinated first time	3	100	100	100 0	0
Revaccinated Group A reverts	3	78	78	100 0	0
Total	3	178	178	100 0	0
Vaccinated first time	12	100	93	93 0	5
Revaccinated Group A reverts	12	78	70	89 7	5
Total	12	178	163	91 5	10

vaccination with Vaccine A. It is of note, moreover, that none of those who were revaccinated showed any accelerated or Koch-like reaction to suggest that any residuum of sensitivity remained.

The duration of sensitivity in Group B was determined in the same manner as described for Group A (0.1 mg of O.T. followed by 1.0 mg if 0.1 mg gave a negative reaction). As may be seen in table 2, 100 per cent of Group B were found to have developed sensitivity to tuberculin three months after vaccination. One year after vaccination, 91.5 per cent of those vaccinated still reacted to tuberculin with a clear-cut, positive skin test, 2.8 per cent had definitely negative reactions, and 5.7 per cent had doubtful reactions. Of the 91.5 per cent who were positive to tuberculin, 73.5 per cent reacted to 0.1 mg of O.T., while the remainder required 1.0 mg to elicit a positive reaction. It is apparent that the number of individuals in Group B who maintained a positive tuberculin sensitivity one year after vaccination is in decided contrast to the results obtained in Group A.

## DISCUSSION

An accumulating experience in the use of BCG vaccine indicates that vaccination with this attenuated tubercle bacillus confers protection against tuberculous infection (1-12). Regardless of the problem of the mechanism of the development of resistance to tuberculosis following BCG vaccination, it appears likely, although not proved conclusively, that production of skin sensitivity to tuberculin is an important criterion for determining whether or not immunity has been enhanced by the procedure. It has been recommended, therefore, that vaccination be repeated until a positive tuberculin reaction results. Birkhaug (8) states, "clinical experience has taught that when allergy produced by BCG vaccination burns out in man, then his tuberculosis resistance falters and re-vaccination is necessary."

Holm (10) believes that effective vaccination must produce a positive tuberculin reaction and that the effect of vaccination lasts only so long as the positive tuberculin reaction persists. If one accepts Holm's and Birkhaug's premises, which it must be emphasized are not conclusively established, then it becomes of considerable importance to know the duration of sensitivity following BCG vaccination.

Holm (10) showed that a majority of vaccinated individuals were positive to 10 mg of tuberculin four years after vaccination whether they existed in a tuberculous milieu or not. Similarly, Birkhaug (8) produced tuberculin sensitivity of long duration following percutaneous administration of BCG vaccine. Rosenthal, *et al* (11) have reported sensitivity following percutaneous vaccination which persisted as long as six to eight years. Aronson (19), using intradermal administration, found that sensitivity probably persisted as long as eleven years.

It is clearly established, therefore, that in the hands of many workers BCG vaccine can confer a long-standing sensitivity to tuberculo-protein. The occurrence of such a short period of sensitivity as that following administration of Vaccine A in the present report was unexpected. The subsequent experience with administration of another vaccine indicates that the variable response is related to some inherent deficiency of the vaccine administered to Group A. The preparation of the two vaccines was essentially the same, as were the environmental conditions of each during the interval from preparation to administration. In fact, Vaccine B was subjected to more rigorous environmental changes than Vaccine A. The method of administration of vaccine was identical for each group.

Several different batches of Vaccine A were administered to Group A and in no instance did the unfavorable results appear to be related to a single ineffective ampule of vaccine. Moreover, the development of the sensitivity in 88 per cent of Group A one month after vaccination indicates that viable organisms were employed.

The possible influence of concentration of the vaccine suspensions cannot be ignored. Vaccine A contained 15 mg of bacteria per cc while Vaccine B contained 20 mg per cc, representing 33 per cent more bacteria per unit of volume in the latter vaccine. Since Vaccine B produced local reactions associated with

a higher level of sensitivity, this suggests that a difference in size of inoculum may have been of importance. The effect of size of inoculum for establishing sensitivity of long duration has been previously demonstrated (15, 16). It should be pointed out, however, that the percutaneous method of vaccination of necessity permits a wide variation in the number of bacteria actually inoculated into each individual.

Forsman (14) has indicated that the manner of vaccination is an important factor in the duration of sensitivity. Since Groups A and B were inoculated by the same technique, this variable can be eliminated from consideration.

A variable potency in the Old Tuberculin preparations used could explain the falling level of sensitivity observed in Group A. While facilities were not available for carrying out as extensive a standardization of tuberculin as Holm (13) recommends, the strengths of three different commercial preparations of O.T. were compared. No significant variation in tuberculin response was observed except when PPD was used. In this instance 0.005 mg. of PPD caused less reaction than 1.0 mg. of O.T. The use of PPD was therefore discontinued early in the study and only freshly prepared Old Tuberculin was administered to both groups. It is unlikely that the loss of sensitivity of Group A can be related to use of a faulty tuberculin.

There are inherent errors in the interpretation of the tuberculin reaction, especially when a low-grade sensitivity is present (4). The tuberculin reactions of Groups A and B were evaluated in as critical a manner as possible. No individual was said to have sensitivity to tuberculin unless an area of erythema measuring at least 5 by 5 mm. was present at the end of forty-eight hours.

Finally, after consideration of the foregoing variables, it becomes probable that a variation in some intrinsic factor in the vaccine accounts for the difference in duration of the induced sensitivity. Jensen (18) has shown the difficulty encountered by one laboratory in an attempt to strike a compromise between a BCG vaccine which produced too great a degree of local reaction and one which failed to produce sufficient reaction to confer sustained sensitivity. Aronson (5) has also suggested that a similar variation in potency of different lots of BCG may exist.

The results of this study appear to support the conclusion that a strain difference of BCG will influence the vaccine's effectiveness as a sensitizing agent. If sensitivity is a reflection of immunity, it is felt that a suitable method of control of the sensitizing potency of BCG vaccine should be set up.

#### SUMMARY

The tuberculin response of two groups of medical students and nurses following administration of BCG vaccine has been studied. In Group A (103 individuals vaccinated with vaccine A) positive skin reactions to tuberculin were observed in 88.3 per cent one month after vaccination, in 79.2 per cent three months later, and in only 10.7 per cent one year after vaccination. Group B (178 individuals) were vaccinated with vaccine B. Three months after vaccination, 100 per cent were positive to tuberculin and 91.5 per cent were positive at the end of one year.



The divergent results obtained with vaccines A and B appear to be related to a strain difference in the BCG used in preparation of the respective vaccines

#### SUMMARY

#### *Variación en la Duración de la Cutisensibilidad a la Tuberculina Producida por Dos Cepas de BCG*

La respuesta a la tuberculina fué estudiada en dos grupos de estudiantes de medicina y enfermeras después de la administración de vacuna BCG. En el Grupo A (103 individuos vacunados con vacuna A), evocáronse cutirreacciones positivas a la tuberculina en 88.3 por ciento al mes de la vacunación, 79.2 por ciento tres meses después, y sólo en 10.7 por ciento al año de la vacunación. El Grupo B (178 individuos) fué vacunado con vacuna B, siendo positivos a la tuberculina 100 por ciento a los tres meses y 91.5 por ciento al año de la vacunación.

Los distintos resultados obtenidos con las vacunas A y B parecen relacionarse con una diferencia en las cepas de BCG usadas para la preparación de las respectivas vacunas.

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# CORRELATION OF NUMBERS OF CUTANEOUS BCG VACCINATION PAPULES AND SUBSEQUENT TUBERCULIN ALLERGY AND TUBERCULOSIS RESISTANCE IN GUINEA PIGS<sup>1</sup>

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## INTRODUCTION

A comparative study was made in 1941 (1) of the development of tuberculin hypersensitivity and specific resistance in guinea pigs inoculated with BCG by the intracutaneous and scarification or multiple puncture methods. It was found that both methods produced a marked degree of tuberculin allergy as well as a significant resistance against a virulent tuberculous infection. It was noted, however, that the multiple puncture method stimulated tuberculin allergy more rapidly and resistance more effectively. On the basis of these findings, the multiple puncture method was applied to man either by the 8-needle fork (2) or the spring-actuated 10-needle apparatus (3). Between 1939 and 1946 more than 10,000 tuberculin-negative children and adults were thus vaccinated in the BCG Clinic at the Municipal Health Center at Bergen, Norway (4). Ninety-nine per cent acquired a positive tuberculin test within two months. The average duration of post-vaccination allergy was found to exceed four years, although occasionally it was lost as soon as one year. As of June 1948, about 80 per cent of the vaccinated group had been periodically followed with annual tuberculin tests and chest roentgenograms. The incidence of pulmonary tuberculosis was one-ninth of that observed among the nonvaccinated general population in Bergen during the same period. Up to the present more than 400,000 persons have been vaccinated throughout Norway. The intracutaneous injection method is used in many clinics while the multiple puncture method is used in others. Proponents of both methods claim equally good results. The latter method, however, is "preferred by about two-thirds of the doctors vaccinating with BCG in Norway," according to Hertzberg (5) and because "the intracutaneous injection may sometimes provoke troublesome local reactions, the percutaneous application (multiple puncture) of BCG has come into vogue." The method has been used exclusively in more than 6,000 BCG vaccinations performed in New York since 1946 under the auspices of the State Department of Health. But since both the injection and multiple puncture and scarification methods are used extensively throughout the world, their comparative efficiency remains a problem of some importance.

Furthermore, the question has been raised whether or not it is necessary to *inflict* as many as forty skin punctures. The following investigation was undertaken to answer that question.

## EXPERIMENTAL

*Materials and methods.* Forty-five normal white albino guinea pigs, weighing  $353 \pm 34.36$  Gm, which failed to react with 10 mg. Old Tuberculin injected intracutaneously, were used.

<sup>1</sup> From the Division of Laboratories and Research, New York State Department of Health, Albany, New York.

A 6 by 5 cm skin area on the right side of linea alba, between the nipple and midsternum, was epilated with electric clippers and thoroughly washed with 95 per cent alcohol and dried with ether

A 10-day-old Sauton culture of BCG (Lot No B-23) showing typical surface growth, was decanted into a harvesting apparatus (6) and the semidry mass of BCG was homogenized and suspended in a dilution fluid that consisted of one part Sauton and three parts physiologic salt solution. The final vaccine contained 20 mg BCG per ml. This suspension gave rise to 47 colonies on Löwenstein's egg medium seeded with a  $10^{-6}$  dilution. Hence the vaccine contained 47 million viable microorganisms per mg semidry weight. This same lot of vaccine was also used in man and gave rise to typical vaccination papules in the skin and positive tuberculin reactions within two months after vaccination.

Thirty guinea pigs, divided into ten equal groups, were vaccinated as follows. Each animal was held tightly by an assistant and a few drops of vaccine were spread evenly across the cleansed epilated skin with a sterile spatula. The sharp point of a 13-gauge sterile needle was pressed tangentially against the taut skin until it penetrated the epidermis at a depth of approximately 2 mm. By lifting the needle point vertically with a swift movement, the skin was torn open at the point where the needle had attached itself to the skin. Care was taken to avert free bleeding, but slight petechial bleeding occurred when the skin was stretched afterwards. While the skin still was held taut, a few more drops of vaccine were spread across the area and allowed to dry for two minutes. The animal was then returned to its cage. In this manner the ten groups of guinea pigs received respectively 1, 2, 4, 6, 8, 10, 15, 20, 30, and 40 skin punctures. The group receiving 6 punctures had 2 rows of 3 punctures each and the groups with 8 and 10 punctures two rows with 4 and 5 punctures in each. The groups receiving 15, 20, 30, and 40 punctures had parallel lines consisting of 5 punctures. An interspace of approximately 5 mm was allowed between each puncture and each line. The remaining 15 guinea pigs were not vaccinated, but were kept under the same conditions as the experimental animals. All were housed in groups of 3, of the same sex, in metal cages (34 by 34 by 25 cm) having closed sides and covered with a metal-framed 1 by 1 cm mesh wire lid.

After three to five days, 1.0 to 1.5 mm wide red punctate lesions appeared which during the following week enlarged into 2 to 4 mm wide and 1 to 2 mm high deeply injected papules. The underlying skin was then palpably indurated and the adjoining axillary and inguinal nodes were slightly enlarged in those animals which had received more than 15 punctures. During the third week the inflammatory reaction began to subside and desquamation followed with resorption of the papular elevations being nearly complete approximately forty days after vaccination. No suppuration occurred in the papules during this period and only a tawny pigmentation or pinhead scars indicated the healed vaccination sites. The lymphatic enlargement persisted for several months without softening or rupture through the overlying skin.

*Post-vaccination tuberculin reactions* The tuberculin tests were performed intracutaneously with Old Tuberculin freshly diluted with saline to contain from 100 mg to 0.001 mg per ml. The reading was made after forty-eight hours and the minimum requirement for a positive reaction was definite induration or edema 10 mm in diameter and 4 mm thick when the skin was folded between caliper prongs. Half of this thickness multiplied by the two diameters of the indurated area ( $2 \text{ by } 10 \text{ by } 10 = 200 \text{ mm}^3$ ) provided an estimate of the volume of the indurated area. When a positive reaction was obtained with 10 mg O.T., the test was repeated with 1.0 mg O.T. to determine the degree of tuberculin hypersensitiveness. The tuberculin tests were repeated at weekly intervals with gradually reduced concentrations of tuberculin during eight post-vaccination

weeks. Table 1 presents the data obtained on the rapidity and degree of tuberculin hypersensitiveness.

It may be seen from the data that the number of papules appears to be directly related to the promptness and degree of reaction to tuberculin and, furthermore, that the maximum reaction occurred in those animals that had received 40 separate intradermal inoculations. Every group that received 8 or more punctures had become tuberculin-positive two weeks following vaccination. The degree of

TABLE 1  
*Tuberculin Reactions*  
*Average Volume of Induration 48 Hours after Intracutaneous Injection of Various Concentrations of Tuberculin*  
(Positive reaction  $\geq 10$  by 10 by 2 mm. (200 mm<sup>3</sup>) induration)  
(3 guinea pigs in each group)

WEEKS AFTER VACCINATION	CONCENTRATION OF OLD TUBERCULIN "MG."	NUMBER OF BCG PAPULES									
		1	2	4	6	8	10	15	20	30	40
1	10	0	0	0	0	0	39	43	74	98	102
2	10	0	0	0	103	261	271	316	451	532	552
3	10	0	0	64	274	261	314	432	468	581	546
4	10	0	0	135	358	393	—	—	—	—	—
5	10	0	112	259	—	—	—	—	—	—	—
6	10	0	184	—	—	—	—	—	—	—	—
7	10	98	148	—	—	—	—	—	—	—	—
8	10	113	—	—	—	—	—	—	—	—	—

Quantitative degree of tuberculin hypersensitiveness											
3	1.0	0	0	0	104	150	250	276	266	278	331
4	0.1	0	0	0	172	178	124	184	168	181	202
5	0.01	0	0	0	154	182	196	222	213	256	270
6	0.001	0	0	0	0	0	0	36	59	108	136
7	0.0001	0	0	0	0	0	0	0	0	45	74
8	1.0	0	0	21	114	189	261	352	382	332	341
8	1.0 BCG OT	0	0	72	150	185	286	383	455	512	542

reactivity of the animals could be determined both by estimating the size of the area of induration and by modifying the dose of O.T. used.

*Response to the inoculation of virulent tubercle bacilli:* Sixty-five days after vaccination the 30 experimental and 15 nonvaccinated control guinea pigs were injected subcutaneously in the right hind leg with 0.0001 mg. of a virulent strain of human tubercle bacilli (No. 33246) from a month-old Löwenstein egg medium culture. This dose gave rise to 1,172 eugonic colonies on a series of Löwenstein egg medium tubes after 10 weeks' incubation. The weight of the immunized animals when challenged was  $621 \pm 60.47$  Gm., and that of the controls  $589 \pm 57.16$  Gm.

Eight weeks later all were retested with 10 mg. O. T. intracutaneously and the reactions read as before. The immunized animals all reacted strongly with

an average induration measuring  $1,819 \pm 654.4 \text{ mm}^3$  and central necrosis occurred in about 50 per cent of these lesions. The most severe reactions were found among the animals that had received fewer than 15 punctures ( $2,278 \pm 566.2 \text{ mm}^3$  induration and  $125 \pm 42.3 \text{ mm}^2$  central necrosis). Those with 20 or more punctures had  $1,236 \pm 447.3 \text{ mm}^3$  induration and  $51.7 \pm 12.8 \text{ mm}^2$  central necrosis. The control group showed  $2,768 \pm 867.9 \text{ mm}^3$  induration and  $261.2 \pm 42.1 \text{ mm}^2$  central necrosis.

The weight of the immunized animals was now  $706 \pm 59.21 \text{ Gm}$ , and that of the control animals  $627 \pm 63.12 \text{ Gm}$ .

The right inguinal lymph nodes were definitely larger in the control than in the immunized groups. Among the latter it was noted that the nodes were larger in the animals that received fewer than 15 punctures than in those with more.

Three control animals succumbed with intercurrent gastrointestinal infection 64, 64, and 65 days after challenge. Of the remaining 12, 6 died with generalized tuberculosis 74, 107, 118, 118, 121, and 132 days after inoculation. The other 6 were killed 163 days after inoculation. Among the immunized groups 6 died with generalized tuberculosis. Two of these had received a single BCG inoculation, 2 others had received but 2 inoculations, and the other 2 had received 4 and 6 inoculations. These animals died at approximately the same time as the controls.

*Measurement of tuberculous hyperplasia.* As previously described (7), necropsy was delayed until the animal had remained for several hours in the refrigerator ( $2^\circ$  to  $3^\circ\text{C}$ ) in order to allow the blood to coagulate. This ensures uniformity in the assessment of the volume and weight of various lymph nodes and organs. The major lymph nodes (table 2) were carefully dissected free from contiguous tissues and their volume was determined by water displacement in specially constructed volumetric cylinders calibrated to 0.001 ml. The volume of the spleen, liver, and lungs was determined in the same manner. Finally, the weight of these organs and the pooled lymph nodes (total lymph nodes) was expressed in per cent of the animal's body weight in order to obtain objective data on the degree of tuberculosis in the immunized and control groups of animals. The completed data were then submitted to statistical treatment for significance according to Fisher's (8) method for comparison of two means.

The data showing the weight of the animals and of lymph nodes, spleen, liver, and lungs for each group of the immunized animals are graphically shown in the figures. For purposes of clarity, the vaccinated animals that had received 1, 2, 4, and 6 inoculations have been pooled (group I). Those that had received 4, 6, 8, and 10 inoculations constitute group II. Those with 8, 10, 15, and 20 inoculations are shown as group III, and those that received a greater number of inoculations have been pooled as group IV.

*Tuberculous hyperplasia in lymph nodes.* The results, which afford a comparison of the volume of the various groups of lymph nodes, have been collected in table 2, with an expression of the probability that the observed differences are significant. It will be noted that the least hyperplasia occurred in group IV, those animals which had received the greatest number of inoculations of vaccine.

TABLE 2

*Tuberculous Hyperplasia in Lymph Nodes from Animals Immunized with 1, 2, 4, 6 (I), 4, 6, 8, 10 (II), 8, 10, 15, 20 (III), 15, 20, 30, 40 (IV) BCG Papules and from Control Tuberculous Infection Animals (V)*

*Statistical Analyses of Volume (in ml) of Nodes from 12 Animals in each Group*

LYMPH NODES		GROUPS OF ANIMALS					PROBABILITY							
		I	II	III	IV	V	I vs V		II vs V		III vs V		IV vs V	
		Volume in ml					<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>
Sup inguinal	Left	0 11	0 11	0 21	0 10	0 21	1 500	0 15	1 372	0 18	0 588	0 59	0 933	0 38
Sup inguinal	Right	0 09	0 01	0 12	0 32	0 81	0 429	0 66	0 473	0 65	10 616	<0 001	13 829	<0 001
Deep inguinal	Left	0 01	0 01	0 01	0 01	0 01	0 220	0 80	0 036	>0 90	0 020	>0 90	0 042	>0 90
Deep inguinal	Right	0 07	0 33	0 16	0 10	0 69	0 056	0 38	1 691	0 12	2 846	0 01	3 555	0 01
Iliac	Left	0 91	0 89	0 57	0 20	0 56	0 588	0 59	0 142	0 88	0 064	>0 90	1 817	0 08
Iliac	Right	1 15	0 95	0 52	0 29	0 78	1 381	0 18	0 681	0 51	1 125	0 27	2 205	0 04
Periportal		1 14	0 71	0 40	0 12	0 97	0 556	0 59	0 858	0 40	0 967	0 07	3 276	<0 01
Retrorenal		1 76	1 75	1 23	0 69	1 16	2 021	0 05	2 651	0 01	0 316	0 75	2 895	0 01
Trach bronch	Left	1 88	1 42	0 82	0 14	1 35	2 791	0 02	0 387	0 71	2 867	<0 01	5 158	<0 001
Trach bronch	Right	1 83	1 52	1 00	0 67	1 38	2 259	0 04	0 848	0 40	2 117	0 04	5 819	<0 001
Cervical	Left	0 15	0 13	0 12	0 11	0 21	1 831	0 08	2 482	0 02	3 520	<0 01	3 756	<0 001
Cervical	Right	0 15	0 16	0 15	0 11	0 22	2 156	0 04	1 303	0 21	1 617	0 12	3 011	<0 01
Axillary	Left	0 08	0 10	0 11	0 09	0 12	1 252	0 21	0 608	0 51	0 311	0 75	0 980	0 35
Axillary	Right	0 09	0 11	0 11	0 09	0 14	1 218	0 22	0 698	0 49	0 686	0 50	1 264	0 22
Total lymph nodes in grams		7 86	7 98	5 53	3 44	7 28	0 965	0 38	0 564	0 59	1 453	0 16	3 628	<0 01
Efficiencies in per cent							0		0		26 7		60 0	

*N B* In Fisher's 1938 tables for distribution of *t* (quotient expressing the deviation as a multiple of its probable error) we observe that a  $P \leq 0 01$  (probability that the observed mean deviation bearing this or smaller values cannot have occurred by chance alone) requires that  $t \geq 2 819$  when each group contains 12 animals or samples. Every difference having absolute significance is italicized in tables 2 and 3.

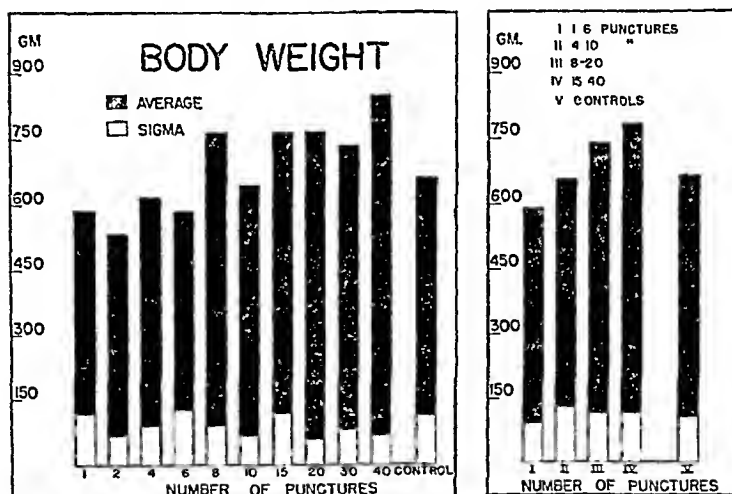


FIG 1 Average body weight at autopsy of vaccinated and control guinea pigs (Left) Single groups of animals vaccinated with 1 to 40 skin punctures (Right) Pooled groups of vaccinated animals

It may also be noted that marked difference existed between the size of the inguinal nodes in the right and left groups. Judged by the criterion of lymph node hyperplasia, therefore, those guinea pigs that had received 10 or fewer injections

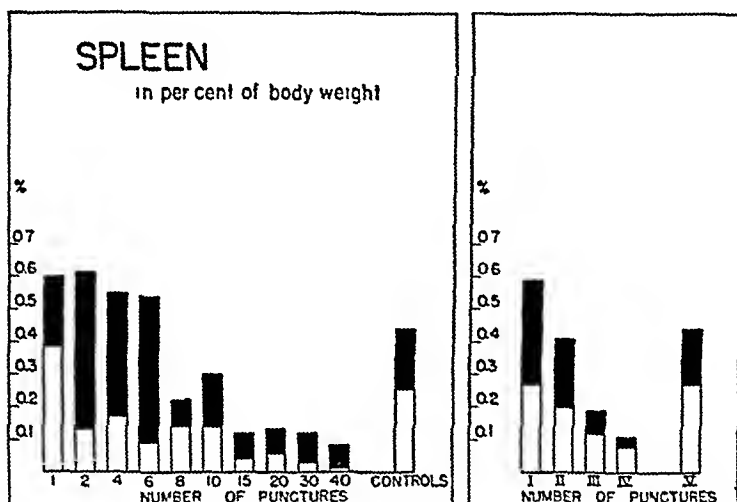


FIG 2 Average weight of spleen expressed in per cent of body weight of vaccinated and control guinea pigs

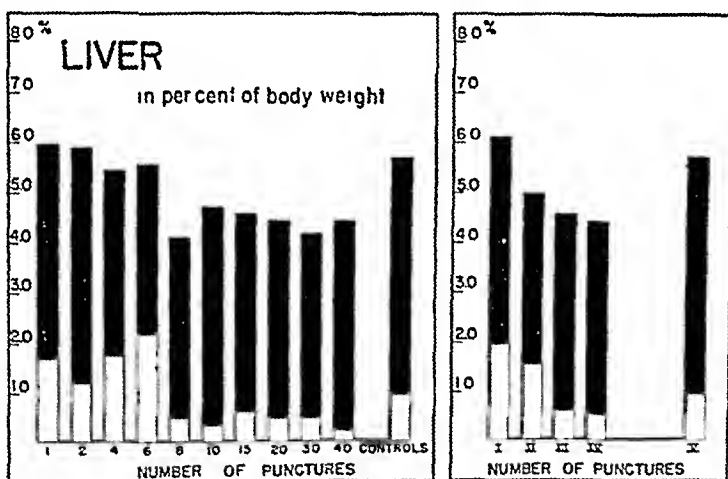


FIG 3 Average weight of liver expressed in per cent of body weight of vaccinated and control guinea pigs

of BCG did not display resistance to the challenging inoculation. The animals which had received a greater number of inoculations showed such resistance.

*Spleen, liver, lungs, and lymph nodes* Similar measurements have been made of the spleen, liver, and lungs of all the animals. The values, again expressed in volume, weight, and in percentage of body weight, have been collected in table 3. It is evident that by these standards the spleens and lungs of the animals

that had received the greater number of vaccination reactions differed significantly from the control animals and from those experimental guinea pigs that had received fewer inoculations. The livers, on the other hand, showed no such

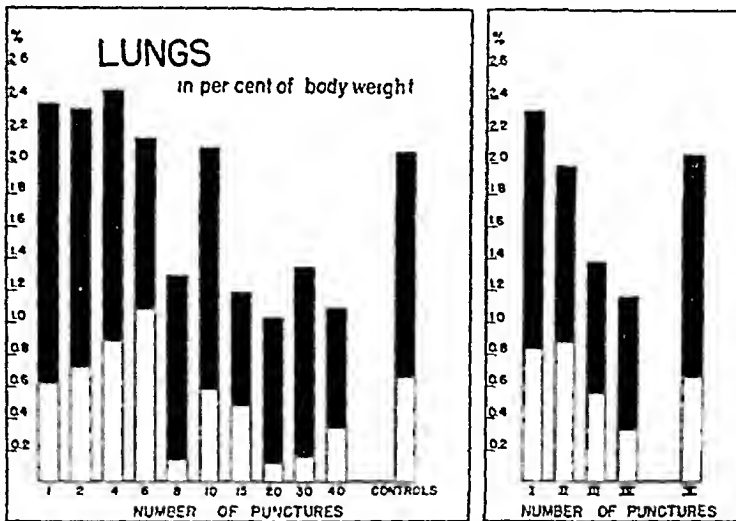


FIG 4 Average weight of lungs expressed in per cent of body weight of vaccinated and control guinea pigs

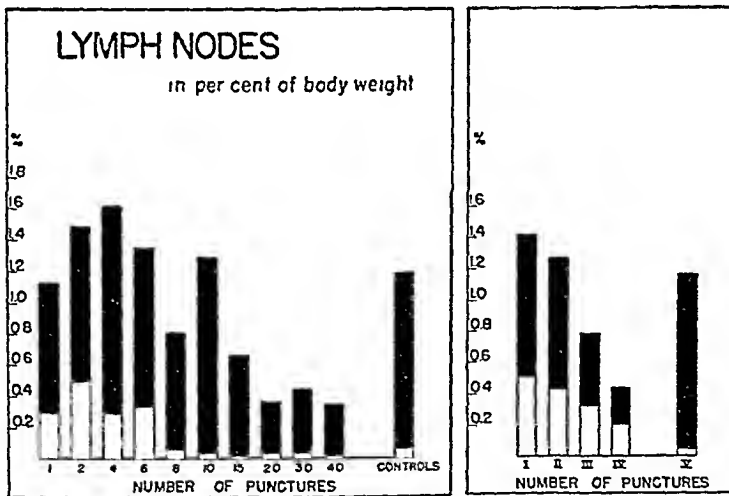


FIG 5 Average weight of pooled lymph nodes expressed in per cent of body weight of vaccinated and control guinea pigs

differences excepting when calculated as percentage of total body weight. By this criterion the lungs also indicated significant deviation.

*Petroff and Steenken score* The lesions have also been graded according to the scheme suggested by Petroff and Steenken (9). The data are summarized in



TABLE 3

*Tuberculous Hyperplasia in Spleen, Liver, and Lungs*  
*Statistical Analyses of Weights, Volumes and Weights Expressed in Percentage of Body Weight*

*12 Animals in Each Group*

ORGANS	GROUPS OF ANIMALS					PROBABILITY							
	I	II	III	IV	V	I \ V		II \ V		III \ V		IV \ V	
	Average					t	P	t	P	t	P	t	P
Body Gm	589	660	735	782	667	1.557	0.15	1.401	0.18	1.457	0.16	2.575	0.01
Spleen Gm	3.16	2.53	1.35	0.81	2.74	1.150	0.27	0.419	0.52	2.622	0.02	4.053	<0.001
Spleen ml	3.10	2.45	1.33	0.83	2.70	1.036	0.07	0.421	0.68	2.516	0.02	3.551	<0.001
Liver Gm	45.73	31.19	32.33	33.77	36.16	0.149	0.59	2.120	0.04	1.671	0.11	1.063	0.20
Liver ml	33.38	29.19	30.96	32.25	33.17	1.367	0.19	1.666	0.12	0.956	0.38	0.792	0.72
Lungs Gm	12.67	12.26	9.90	8.75	13.41	0.566	0.59	0.802	0.41	2.568	0.02	2.595	<0.01
Lungs ml	14.68	14.40	12.41	10.89	17.21	1.651	0.11	1.691	0.11	2.972	0.01	4.915	<0.001

Weights expressed in percentage of body weight

Spleen per cent	0.58	0.40	0.19	0.11	0.44	2.303	0.03	0.375	0.71	2.612	0.02	5.027	<0.001
Liver per cent	6.04	4.91	4.40	4.39	5.56	1.328	0.20	1.220	0.25	3.653	0.01	3.750	<0.001
Lungs per cent	2.31	1.98	1.39	1.16	2.06	0.980	0.38	0.247	0.75	2.631	0.02	4.599	<0.001
Lymph nodes per cent	1.41	1.27	0.78	0.46	1.10	2.002	0.05	0.503	0.75	1.642	0.12	5.112	<0.01

Efficiencies in per cent

0		0		18.2		51.8	
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TABLE 4

*Macroscopic Scoring of Tuberculous Involvement in Vaccinated and Control Guinea Pigs*  
*(Ad modum S. A. Petroff and W. Steenken, Jr., J. Immunol., 1930, 19, 79)*

ANIMAL GROUPS	NUMBER OF ANIMALS	TUBERCULOUS INVOLVEMENT							
		++++		+++		++		+	
		Num ber	Per cent	Num ber	Per cent	Num ber	Per cent	Num ber	Per cent
Control	12	4	33.3	6	50.0	2	16.7	0	0
Vaccinated I	12	2	16.7	10	83.3	0	0	0	0
Vaccinated II	12	1	8.3	8	66.7	3	25.0	0	0
Vaccinated III	12	0	0	3	25.0	3	25.0	6	50.0
Vaccinated IV	12	0	0	0	0	0	0	12	100.0
Vaccinated									
Punctures 1	3	1		2		0		0	
Punctures 2	3	0		3		0		0	
Punctures 4	3	0		3		0		0	
Punctures 6	3	1		2		0		0	
Punctures 8	3	0		1		2		0	
Punctures 10	3	0		2		1		0	
Punctures 15	3	0		0		0		3	
Punctures 20	3	0		0		0		3	
Punctures 30	3	0		0		0		3	
Punctures 40	3	0		0		0		3	

+ = tuberculous lesions at the site of inoculation, with or without lymph node involvement, with few tubercles in lungs and spleen

++ = tubercles in 2 or 3 organs, such as spleen, liver, lungs, and lymph nodes

+++ = generalized tuberculosis, as well as extensive active disease, such as tuberculous pneumonia

++++ = fulminating and generalized tuberculosis, with multiple and large infarcts in spleen and liver, multiple cavernous and confluent tuberculosis in lungs, with heavy involvement of lymph nodes, ruptured spleen, and allergic phenomena

table 4 It may be seen that one-third of the control animals had fulminating and generalized tuberculosis (4+) with suppuration at the site of inoculation. Multiple and confluent infarcts in the spleen and liver, multiple cavernous and confluent tuberculosis in the lungs, and generalized caseonecrotic hypertrophy of lymph nodes were common. Half of the control animals showed generalized tuberculosis with somewhat less involvement (3+) and the rest showed tuberculosis of the lymph nodes, spleen, liver, and lungs.

The animals which had been vaccinated with from 1 to 8 inoculations did not differ significantly from the controls but those which had received 10 or more showed less tuberculosis, this was still more pronounced in the animals that had received 15 inoculations. In them only tuberculosis in the regional lymph nodes (1+) and an occasional discrete tubercle in the spleen or lung were found. The results confirmed the measurements of organ size and weight and allergy in showing the improved status of the animals that had received the largest number of vaccinations.

#### DISCUSSION

The data leave little room to doubt that in the case of experimental tuberculosis in the guinea pig the promptness and extent of tuberculin allergy is related to the size of the BCG vaccination and that resistance to infection increases with the number of individual inoculations and the number of BCG microorganisms inoculated. In these experiments the duration of allergy has not been measured. It will be remembered that Tornell (10) found that the duration of tuberculin allergy was also related to the size of the vaccination reaction. It would seem, therefore, that the larger number of papules currently being recommended for percutaneous vaccination is thoroughly supported by experimental evidence.

#### SUMMARY AND CONCLUSIONS

The multiple puncture method of BCG vaccination produced in guinea pigs the most rapid and intense tuberculin allergy when 15 or more punctures were made through skin moistened with 20 mg per ml BCG vaccine. The best tuberculin allergy was produced by 40 BCG vaccination papules.

A significant resistance to a virulent tuberculous infection was acquired by guinea pigs having received 15 or more punctures. The most effective specific immunity was produced by 40 BCG vaccination papules.

It is recommended, therefore, that the practice of 30 to 40 percutaneous punctures in BCG vaccination of both children and adults be continued in order to produce the most rapid allergy and durable resistance to tuberculous disease.

#### SUMARIO Y CONCLUSIONES

*Correlacion entre el Numero de Papulas Cutáneas en la Vacunacion BCG y la Subsiguiente Alergia a la Tuberculina y Resistencia a la Tuberculosis en el Cobayo*

La técnica de la multipunción para la vacunación con BCG produjo en los cobayos la más rápida e intensa alergia tuberculínica cuando se hacían quince o más punciones a través de piel humedecida con 20 mg por cc de vacuna BCG.

La mejor alergia a la tuberculina fué producida por cuarenta pápulas en la vacunación con BCG

Resistencia significativa a una infección tuberculosa virulenta fué adquirida por cobayos que recibieron quince o más punciones. La más efectiva inmunidad específica fué producida por cuarenta pápulas de vacunación BCG

Recomiéndase, por lo tanto, que, a fin de producir la alergia más rápida y resistencia duradera a la afección tuberculosa, continúe, tanto en niños como adultos, la costumbre de hacer treinta a cuarenta punciones percutáneas en la vacunación con BCG

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# LUNG TRAUMA AT PNEUMOTHORAX INDUCTION<sup>1</sup>

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## INTRODUCTION

Induction of artificial pneumothorax is a simple procedure which in the great majority of instances is attended by little discomfort and no complications. Most physicians experienced in pneumothorax therapy, however, have observed serious and at times alarming complications at induction, the most important being air embolism and perforation of the lung.

The literature indicates the considerable difference of opinion which exists concerning the frequency of lung rupture at the time of pneumothorax induction. The early workers, Brauer (1), Robinson and Floyd (2), Balboni (3), and others, considered traumatic pneumothorax avoidable with good technique. Morgan (4), on the other hand, believed as long ago as 1914 that the first intrapleural readings obtained are those of a traumatically induced space. There has been much controversy regarding the type of needle which might cause or prevent lung puncture (Jones (5), Tchertkoff and co-workers (6, 7, 8, 9)). Karan (10) observed roentgenographic evidence of rupture of the lung following induction of pneumothorax in 9 of 70 patients, or 13 per cent, and Rubin (11) stated in 1937 that "lung injury is the rule rather than the exception in pneumothorax treatment, particularly at the time of induction." Rubin pointed out the fact that often rupture cannot be verified clinically and that in most instances it is not followed by immediate serious consequences. These are usually lung perforations of the "closed," not valvular, variety which close quickly aided by the relaxing effect of the pneumothorax. A pneumothorax space has often been demonstrated by roentgenography or fluoroscopy after a supposedly unsuccessful attempt at induction. Examples of this have been cited by Ornstein and co-workers (12). Using the formula of Coryllos (13), Ornstein and his associates (12) calculated the volume of gas present in the pleural cavity twenty-four hours after induction, in 5 cases they found an increase over the volume of air which had been injected of from 115 to 2,170 cc. Alexander (14) has stated that "a puncture of the visceral pleura with the pneumothorax needle is largely preventable." Ustvedt (15) believes injury to the lung during induction to be a "very common occurrence." Mattil and Jennings (16) reviewed a large series of traumatic pneumothoraces and found that lung perforation had occurred at induction in 2 per cent of cases with unilateral pneumothorax and in 10 per cent of inductions in cases where pneumothorax was already present on the other side. In the majority of the unilateral cases, symptoms were slight or absent. In most of the bilateral cases, symptoms were severe enough to require needle deflation or catheter drainage, and in the bilateral group the lung rupture was fatal in 5 instances.

The present writers were stimulated to reinvestigate the problem of lung trauma at pneumothorax induction by the occurrence of a nearly fatal lung perforation which was seen at the Montefiore Hospital Sanatorium.

H. D., a 44-year old man with far advanced bilateral fibrocaverculous pulmonary tuberculosis, had been receiving left artificial pneumothorax treatment for two years.

<sup>1</sup> From the Montefiore Hospital Country Sanatorium, Bedford Hills, New York.

The pulmonary collapse was complicated by apical adhesions which could not be severed. The therapy was clinically effective, however, and because of extensive contralateral disease and the inadvisability of performing thoracoplasty the pneumothorax had been maintained. The lesions in the right lung progressed and excavated. On July 26, 1948 right artificial pneumothorax was induced. No difficulty was encountered at induction and pleural readings with good oscillations were obtained immediately. The initial pressures were  $-14$   $-9$  cm. of water, final pressures after administration of 250 cc. of air were  $-10$   $-4$ . The patient was seen three hours later and appeared comfortable. Six hours after induction he experienced increasing dyspnea and preparations were made to decompress the right pleural cavity. As the decompression needle was about to be inserted, the patient's condition suddenly became alarming. His dyspnea increased, he was cyanotic, and there was tachycardia with a rate of 140 per minute. A 19-gauge needle was inserted into the right pleural cavity, pressures, of  $-10$   $+10$  were recorded, and air was removed. A few minutes later the patient was severely dyspneic, intensely cyanotic, his radial pulse was almost imperceptible, and his skin was cold and clammy. He became comatose and appeared moribund. A 19 gauge needle was immediately inserted into the left pleural space. Positive pressure was recorded here also ( $-40$   $+10$ ) and the left pleural space was decompressed. The patient was placed in an oxygen tent, and air under pressure was repeatedly aspirated from both pleural cavities. His condition improved and after removal of 2,000 cc. of air from the left chest the pressure readings on this side became and remained negative. The right lung continued to leak air and to build up tension in the right pleural cavity. After removal of about 7,000 cc. of air from that side, with pressures repeatedly returning to highly positive after each aspiration, an indwelling needle was inserted with subaqueous drainage. Continuous decompression was maintained for eleven hours, at the end of which time observation indicated closure of the perforation. One gram of streptomycin and 500,000 units of penicillin were instilled into the pleural space and the needle was removed. The patient's subsequent course was uneventful. No attempt was made to maintain the pneumothorax on the right side, and the patient was given streptomycin intramuscularly in dosage of one gram daily for two months. This was followed by regression of the lesions in the right lung and sputum conversion. The left pneumothorax was continued.

This dramatic occurrence resulted from perforation of the right lung at the time of induction. One may speculate that removal of the support of the chest wall by the creation of a pneumothorax permitted an emphysematous bleb to rupture or an adhesion to tear at its visceral junction, but actual trauma to the lung by the induction needle is the more likely explanation.

In 29 inductions performed at Sea View Hospital, Selikoff and Tcherthoff (9) noted appreciable dyspnea in 40 per cent, and 14 per cent of their patients required pleural decompression following induction of pneumothorax. These authors postulated that every induction is accompanied by traumatic pneumothorax and that injury to the lung is unavoidable. They attempted to demonstrate this by taking radiograms of the chests of patients after needling the pleural space without introducing air. In their clinical material and with their technique (6, 7, 8, 9) they did in fact show that every induction was first a traumatic one. In 19 consecutive cases simple needling of the pleural space produced pulmonary collapse in every instance, varying in extent from 5 to 90 per cent. On the basis of these findings, they recommended that pneumothorax should be induced by lung puncture purposefully produced with a fine-gauge needle. They consider this method least likely to produce a severe tear of the lung. In reviewing their data (7), it is apparent that the intrapleural pressures recorded were unsatisfactory in 5 of the 19 cases. Furthermore, the clinical material at

Sea View Hospital, a municipal institution, is probably not typical of sanatorium patients generally. Unpublished observations on a large number of pneumothorax inductions performed at the Montefiore Hospital Sanatorium during the last two years reveal a much lower incidence of significant lung trauma. In patients with a free pleural space, initial pneumothorax treatment was followed by symptoms and fluoroscopic findings indicative of definite lung perforation in 3.33 per cent, an incidence one-twelfth that reported by Selkoff and Tchertkoff.

The present investigation has been conducted to evaluate the validity of the assumption that significant lung damage is unavoidable during pneumothorax induction.

#### MATERIAL AND METHODS

A series of 23 consecutive unselected sanatorium patients who required pneumothorax therapy for control of active pulmonary tuberculosis forms the basis of this study. Thirteen of them were females and 10 males. Their ages ranged from 19 to 42 years. Twenty had moderately advanced tuberculosis and 3 had far advanced disease. In 8 the lesions were unilateral, in 15 bilateral, and 22 had patent cavities (table 1).

The patients were prepared for induction of pneumothorax in the usual manner, and the induction needle was inserted carefully until intrapleural readings with respiratory oscillations were obtained on the manometer.<sup>2</sup> Patients were not urged to breathe deeply. When readings had been obtained, the needle was removed. No air was introduced into the pleural cavity. A postero-anterior roentgenogram of the chest was made in expiration three or six hours later and again twenty-four hours after pleural puncture. In 6 patients (Cases 18, 19, 20, 21, 22, and 23, table 1) expiration films were also made in left anterior and right anterior oblique projections. The films were then inspected for evidence of pneumothorax. Some patients were also fluoroscoped, but expiration films have been found to be more satisfactory, especially in thick-chested individuals. After the twenty-four-hour film had been obtained, pneumothorax was induced and at this time air was allowed to enter the pleural cavity from the pneumothorax apparatus. All punctures were performed with a Fischer<sup>3</sup> induction needle. It is felt that similar results could probably be obtained with a 19-gauge short-beveled needle. However, a sharp cutting-edge cannula and dull obturator combination, like the Fischer, Solomon, or Kuss induction needle, is a little safer for those without great experience because there is less danger of grossly overshooting the mark in the process of forcing a dull needle through thick skin or endothoracic fascia.

#### RESULTS

The needling of the space without introduction of air produced the following results. None of the 23 patients became dyspneic. In 21 of the 23 no pneumo-

<sup>2</sup> A Zavod or a Davidson pneumothorax apparatus was used in all cases.

<sup>3</sup> This consists of a 14-gauge sharp outer cannula and a 17-gauge 3-inch needle with blunt tip which is inserted through the cannula for the pleural puncture. (B-D Catalogue No. LL1, p. 23, items nos. 475 LNRA and 475 LNRB. Becton, Dickinson and Co., Rutherford, New Jersey.)

thorax space could be seen on expiration films taken three, six, and twenty-four hours later. All 23 patients had unobliterated pleural spaces as shown by the intrapleural readings (table 1) and by the successful induction of pneumothorax performed twenty-four hours later. One of the patients, Case 1, had a traumatic pneumothorax requiring decompression after the second pleural puncture, but not after the first. Her intrapleural pressures were  $-13$   $-9$  cm of water at the

TABLE 1  
*Intrapleural Pressures in 23 Consecutive Initial Pleural Punctures, with and without Administration of Air*

CASE NUMBER	ROENTGENOGRAPHIC CLASSIFICATION OF LESIONS			INTRAPLEURAL READINGS			
	Distribution	Extent	Predominant Types	First needling*	Second needling†		
				Reading in cm of H <sub>2</sub> O	Reading in cm of H <sub>2</sub> O	Amount of air in cc.	Reading 10 cm of H <sub>2</sub> O
1 H S	Unilateral	Mod adv	Caseocavernous	$-13$ $-9$	$-13$ $-9$	200	$-5$ $-3$
2 J B	Bilateral	Mod adv	Caseocavernous	$-8$ $-6$	$-8$ $-6$	200	$-4$ $-2$
3 A W	Bilateral	Mod adv	Fibrocaseocavernous	$-10$ $-6\frac{1}{2}$	$-12$ $-8$	300	$-6$ $-4$
4 L C	Bilateral	Far adv	Fibrocaseocavernous with contralateral pleuritis	$-10$ $-5\frac{1}{2}$	$-7$ $-3$	250	$-5$ $-2$
5 M A	Bilateral	Mod adv	Caseocavernous	$-12$ $-10$	$-13$ $-9$	250	$-8$ $-2$
6 A C	Unilateral	Mod adv	Caseocavernous	$-10$ $-7$	$-10$ $-6$	300	$-8$ $-4$
7 S S	Unilateral	Mod adv	Caseocavernous	$-10$ $-7$	$-10$ $-8$	300	$-6$ $-5$
8 L F	Bilateral	Mod adv	Caseocavernous	$-8$ $-6$	$-5$ $-3$	250	$-4$ $-2$
9 F D	Bilateral	Mod adv	Caseocavernous	$-13$ $-8$	$-13$ $-7$	300	$-10$ $-5$
10 S K	Bilateral	Mod adv	Caseocavernous	$-7$ $-4$	$-8$ $-4$	125	$-5$ $-2$
11 A R C	Unilateral	Mod adv	Caseocavernous	$-11$ $-10$	$-11$ $-5$	250	$-7$ $-1$
12 K H	Unilateral	Mod adv	Caseocavernous	$-7$ $-4$	$-7$ $-2$	250	$-5$ $-1$
13 B H	Bilateral	Mod adv	Fibrocaseocavernous	$-9$ $-7$	$-12$ $-10$	300	$-7$ $-2$
14 A L	Bilateral	Mod adv	Fibrocaseocavernous	$-12$ $-8$	$-7$ $-3$	300	$-7$ $-2$
15 W P	Unilateral	Mod adv	Caseocavernous	$-9$ $-5$	$-10$ $-8$	300	$-9$ $-6$
16 F K	Bilateral	Mod adv	Fibrocaseocavernous	$-8$ $-5$	$-9$ $-5$	250	$-5$ $-2$
17 E T	Bilateral	Mod adv	Caseocavernous	$-12$ $-11$	$-12$ $-9$	250	$-7$ $-5$
18 E L	Bilateral	Far adv	Fibrocaseocavernous with bilateral pleuritis	$-6$ $-4$	$-7$ $-4$	250	$-6$ $-3$
19 R W	Unilateral	Mod adv	Caseocavernous	$-9$ $-7$	$-8$ $-7$	250	$-5$ $-3$
20 M T	Unilateral	Mod adv	Caseocavernous	$-5$ $-3$	$-5$ $-3$	300	$-3$ $-1$
21 H S	Bilateral	Mod adv	Fibrocaseocavernous	$-11$ $-7$	$-10$ $-5$	250	$-5$ $-3$
22 S L	Bilateral	Far adv	Fibrocaseocavernous	$-11$ $-7$	$-13$ $-7$	300	$-7$ $-3$
23 I S	Bilateral	Mod adv	Fibrocaseous with contralateral pneumothorax	$-10$ $-5$	$-13$ $-5$	150	$-11$ $-4$

\* No air given

† Performed 24 hours later. Air was administered at this time

‡ 'Traumatic pneumothorax'

time of experimental needling, and roentgenograms three and twenty-four hours later showed no pneumothorax space. After the twenty-four-hour film had been taken pressures were again found to be  $-13$   $-9$  (table 1) and at this time air was given. Lung perforation followed the latter puncture.

Two of the 23 patients showed the presence of air intrapleurally on the roentgenograms obtained after needling alone (Cases 3 and 4, table 1). The extent of collapse was 10 per cent of the right upper lobe in Case 3 and 20 per cent of the right upper lobe in Case 4. In these 2 cases traumatic pneumothorax had undoubtedly occurred. No symptoms were noted in either patient.

The question arises as to how much air must be in a pleural space for it to be

visible? Tehertkoff (6) states that less than 150 cc cannot be detected by any roentgenographic technique. Accordingly, 12 patients were examined roentgenographically twenty-four hours after induction with 150 to 300 cc of air. In all of these patients the pneumothorax space was clearly visible on an expiration film made twenty-four hours later (table 2). This is not inconsistent with Tehertkoff's estimate. Visualization of amounts less than 150 cc was not attempted. Left anterior oblique and right anterior oblique films were made in expiration in 6 cases (Cases 7, 8, 9, 10, 11, and 12, table 2) in addition to the postero-anterior expiration films. The pneumothorax space was visualized in all views.

TABLE 2  
Amount of Pneumothorax Collapse Visualized 24 Hours after Induction

CASE NUMBER	AIR ADMINISTERED cc	COLLAPSE VISUALIZED IN EXPIRATION
		per cent
1 M A	250	25*
2 A C	300	20
3 J B	200	less than 5†
4 E T	250	15*
5 F K	250	15
6 M H	300	30†
7 E L	250	20*
8 R W	250	15
9 M T	300	10
10 H <sub>3</sub> S	250	10*
11 S L	300	20
12 I S	150	10*

\* Indicates per cent collapse of upper lobe only

† Indicates per cent collapse of lower lobe only

#### DISCUSSION

As has been noted, in all 12 patients given 150 to 300 cc of air, a pneumothorax was visualized roentgenographically twenty-four hours later (table 2). With identical technique, but without introduction of air into the pleural space from without, 21 of 23 showed no pneumothorax space. If the latter 21 suffered trauma to the lung, it was probably of a degree insufficient to permit leakage of 150 cc or more of air. The possibility that smaller amounts than this entered the pleural space from the lung cannot be excluded. Roentgenograms in other projections might have shown this, but in 6 cases oblique projections were made and failed to do so.

An alternative explanation is conceivable. It might be argued that, in the cases where air was given, the space visualized twenty-four hours later actually contained more than the amount of air which entered from the outside, possibly lung leakage *plus* the air administered, and that the amount of air necessary for visualization is really much greater than stated. If this were so, perforation of the visceral pleura could have occurred in all of our 23 patients. But for some reason this hypothetical leakage is always less than in the cases where air is given and a space is visualized. Perhaps this is a result of earlier closure of a perforation when



the pleural surfaces are not separated by injected air. On the other hand, it would seem that the injection of air would of itself tend to close a small rupture by decreasing the vacuum in the space.

There is little doubt that lungs which are the seat of very extensive disease are more likely to be traumatized by a pneumothorax needle. Bilateral lesions, emphysema, and contralateral collapse by pneumothorax or thoracoplasty make the hazard still greater. The less diseased portions of the lung are expanding more fully with each inspiration in order to compensate for reduced ventilatory capacity, and it is over these areas that the induction needle is inserted. Furthermore, when a perforation does occur in a lung which contains very extensive fibrosis and emphysema, its closure is impeded by the decreased elasticity of the organ. Most of the cases needled and reported herein were not of this type but were of a character for which pneumothorax is usually used in current practice. In these, the theory that "traumatic induction" is inevitable and unavoidable was not confirmed.

In some instances, despite careful technique, the lung is perforated at induction. This may produce no symptoms. Every patient in whom a space is not demonstrated by manometer readings should have a roentgenogram of the chest in expiration twenty-four hours after needling. A pleural space may be present and may then be visualized because of escape of air through a traumatized visceral pleura.

Further investigation along the lines indicated and using different roentgenographic projections would be helpful in establishing correlation between the amounts of air administered and the roentgenographic appearance following pneumothorax induction.

#### SUMMARY AND CONCLUSIONS

1 With the method of pneumothorax induction employed, trauma to the lung was proved to have occurred in only 2 of 23 cases. In neither instance were recognizable symptoms noted and the collapse was discovered solely by roentgenography.

2 In 21 of 23 cases it was not possible to demonstrate escape of air from the lung following pleural puncture in amounts sufficient to be seen on expiration radiograms up to twenty-four hours later.

3 A pneumothorax space was invariably demonstrated by identical roentgenographic technique when air in amounts of 150 to 300 cc. was injected.

4 In the majority of patients with unilateral or bilateral moderately advanced pulmonary tuberculosis, the conventional method of pneumothorax induction with a blunt needle does not cause trauma to the lung of sufficient degree to permit escape of air demonstrable by available roentgenographic methods.

#### SUMARIO Y CONCLUSIONES

##### *Traumatismo Pulmonar en la Inducción del Neumotórax*

1 Con la técnica empleada para la inducción del neumotórax, sólo en 2 de 23 casos se comprobó que había ocurrido traumatismo pulmonar. Ni en uno ni en

otro caso hubo síntomas reconocibles y el colapso fué descubierto solamente por la radiografía

2 En 21 de 23 casos no fué posible observar, después de la punción pleural, escape de aire en cantidades suficientes para mostrarse en las radiografías tomadas a la expiración hasta veinticuatro horas después

3 Un espacio neumotorácico fué invariablemente revelado con una técnica roentgenográfica idéntica al inyectar aire en cantidades de 150 a 300 cc

4 En la mayoría de los enfermos con tuberculosis pulmonar uni- o bilateral moderadamente avanzada, la técnica convencional de inducción del neumotórax con una aguja roma no ocasiona suficiente traumatismo pulmonar para poder observar escape de aire con las actuales técnicas roentgenográficas

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# A CLINICAL STUDY OF THE TOXIC EFFECTS OF DIHYDROSTREPTOMYCIN AND STREPTOMYCIN<sup>1</sup>

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## INTRODUCTION

Dihydrostreptomycin is prepared by the catalytic hydrogenation of streptomycin. It was first described by Peek, Hoffhine, and Folkers (1) in 1946. *In vitro* studies showed that this new drug had about the same antimicrobial spectrum as streptomycin and about the same degree of potency. Subsequent animal and clinical trials suggested that the toxicity might be significantly lower, particularly with respect to "hypersensitivity" reactions and embarrassment of vestibular function (2, 3, 4). More recent studies have yielded conflicting data, some of which seem to show a relatively earlier onset of vestibular damage with streptomycin, but with roughly the same incidence of toxicity with both drugs by the time treatment was concluded (5). Marked hearing loss in as many as 25 per cent of the patients has been reported, occurring two to three weeks after dihydrostreptomycin was discontinued (5). An "explosive" type of vestibular damage has also been seen recently, developing suddenly as early as forty-eight hours after treatment was started with doses presumed to be safe (6).

In most clinical studies with dihydrostreptomycin, the amount of toxicity produced was compared with that which had been produced in the past with equivalent doses of streptomycin. Current opinion about the effect on the vestibular apparatus of two or three grams of streptomycin is based largely on the experience gained from 1945 to 1947, when these doses were widely employed in the treatment of tuberculosis. It was thought desirable to test dihydrostreptomycin against currently produced streptomycin due to the possibility that earlier observations of the toxic effects of large doses of streptomycin might not at present apply.

When the damaging effects of these two drugs are compared in a small series, it is necessary to use a dose high enough to produce a significant amount of toxicity with at least one of the drugs. One gram of streptomycin daily is the usual dose currently employed in the treatment of most forms of tuberculosis. This dose is known to produce vestibular damage in only about 5 per cent of the patients. Thus a very large series of cases would have to be treated with this dose of dihydrostreptomycin before comparable results could be obtained. The alternative method is to treat two groups of patients with dihydrostreptomycin and streptomycin in large enough doses and for a sufficient length of time to produce a significant amount of toxicity in a small series.

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Early in November 1948 a quantity of dihydrostreptomycin<sup>3</sup> was made available to the Tuberculosis Service at Freedmen's Hospital for toxicity studies. To provide a "control" group, an equivalent amount of streptomycin<sup>4</sup> was obtained. Careful examinations for toxic effects would be carried out at regular intervals.

#### MATERIALS AND METHODS

Twenty patients were selected for study and were divided into two groups of 10 each in such a manner that age, weight, and sex were roughly the same in

TABLE 1  
*Comparison of Streptomycin-treated and Dihydrostreptomycin-treated Groups*

	TOTAL	STREPTOMYCIN	DIHYDRO STREPTOMYCIN
Number of patients	19	10	9*
Average age (years)	27.9	27.9	27.9
Average weight (pounds)	121.0	121.0	120.9
Sex			
Male	6	4	2
Female	13	6	7
Stage of disease			
Far advanced	14	9	5
Moderately advanced	4	1	3
Minimal	1	0	1
History of streptomycin treatment			
Within 6 months of study	2	1	1
More than 6 months prior to study	6	5	1

\* One patient assigned to the dihydrostreptomycin group died after fifty-seven days of treatment without having shown any signs of toxicity, and is not included in this analysis.

both groups. One group was then selected for dihydrostreptomycin treatment, the other to receive equal doses of streptomycin (table 1).

Each patient received 3.0 Gm. of drug daily. This was given in divided doses of 1.0 Gm. every eight hours. Each gram was diluted with distilled water so that each ml. contained 500 mg. The injection was given in the upper outer quadrant of the gluteal region. Because of the large doses of the drug being used, treatment was stopped at the first definite indication of vestibular damage, either subjective or objective, unless the patient's need for and apparent response to treatment justified its continuation.

The toxic symptoms which were a basis for discontinuing either drug were as follows:

1. The syndrome of vestibular dysfunction characterized by
  - a. *Ataxia*—patient unable to walk alone in extreme cases. If they are able to walk, they walk with a broad base and are unable to walk a straight line.
  - b. *Nausea and vomiting*.
  - c. *Visual dysfunction*—initial difficulty in focusing particularly for near vision.
  - d. *Dizziness*—aggravated by accelerating or turning movements.

<sup>3</sup> Obtained from Merck & Company, Inc.

<sup>4</sup> Provided by the Central Coordination and Analysis Office of the Tuberculosis Study Section, National Institutes of Health.

- e *Tinnitus*—ringing, roaring, or hissing sound in either ear
- f *Spontaneous nystagmus*—regular rhythmic movement of the eyeballs in lateral, vertical, or rotary directions with definite fast and slow components
- 2 Deafness increasing under treatment
- 3 Severe blood dyscrasias
- 4 Exfoliative dermatitis

In addition to the above, pain and local reaction at the site of injection and drug fever were watched for and recorded when they occurred but were not considered as a basis for stopping treatment

All patients were questioned and examined daily for symptoms and signs of toxicity. Great care was taken to see that no "leading questions" were asked of these patients concerning any of their symptoms, particularly those which might be considered evidence of vestibular damage. No specific questions were asked, for instance, concerning dizziness unless the patient had already volunteered the information that he was dizzy.

Prior to the administration of either drug, determinations of the blood non-protein-nitrogen, complete hemograms, urinalyses, audiograms, caloric stimulation, and roentgenograms of the chest were obtained and were repeated at regular intervals thereafter. One of us has modified the caloric stimulation test devised by Glorig and Fowler (7) in order to make it convenient for large numbers of patients to be tested.

#### *Modified Glorig and Fowler Caloric Stimulation Test*

##### *Equipment*

- 1 Back boards at 30° angle
- 2 One gallon thermos jug with spigot
- 3 Rubber tubing
- 4 Glass tip
- 5 Centigrade thermometer enclosed in a glass tube so that the water flows past the bulb
- 6 Floor stands for intravenous administrations
- 7 Stop watch
- 8 20 cc syringe with short rubber tubing attached
- 9 Basins, towels, et cetera

##### *Procedure*

- 1 The patient is positioned so that he lies on the back rest with the head at an angle of 30° with the floor
- 2 The thermos jug is filled with water adjusted to 30° C and hung from the intravenous stand about eighteen inches above the patient's head. Tubing is connected so that water flows past the thermometer bulb and out the glass tip almost immediately thereafter
- 3 The glass tip is introduced into the right external ear canal and the canal is irrigated with water at 30° C for exactly forty seconds by the stop watch. The duration of the nystagmus produced is then timed from the start of stimulation
- 4 If no response is produced, the test is repeated in the left ear
- 5 If no response is produced by water at 30° C in either ear, 20 cc of ice water (0° C) is run into the right ear slowly by means of a syringe with rubber tubing tip. The duration of the response is recorded

##### *Interpretation*

- 1 If nystagmus lasting longer than 100 seconds is produced by 30° C in either ear, the response is normal

- 2 If no nystagmus is produced by 30° but some nystagmus, however transient, is produced by ice water, the response is diminished
- 3 If no nystagmus is produced by either ice water or water at 30° C the response is absent

These three categories are mutually exclusive and all test results fall into one of these categories

TABLE 2  
*Laboratory Data Obtained on Patients in Both Groups*

PATIENT	BLOOD NON-PROTEIN NITROGEN, MG PER 100 CC		URINALYSIS		NEUTROPHIL LYMPHOCYTIC RATIO		LEUKOCYTES PER CU MM		EOSINOPHILS PER 100 LEUKOCYTES	
	Before	After	Before	After	Before	After	Before	After	Before	After
S M	48	23	Neg	Neg	10 5/ 2 8	63 5/33 5	13,700	7,200	0 5	0 0
D S	48	22	Neg	Neg	60 5/36	69/30	9,200	13,150	3 5	1 0
J B	32	25	20 leukocytes per cu mm	Neg	78 5/19 5	67/29	6,650	7,700	1 5	3 0
B W	30	26	Neg	Neg	58/40	65 5/33 5	5,550	5,000	1 0	1 0
J M	51	24	Neg	Neg	80/18	70/30	8,850	12,700	0 5	0 0
I A	30	23	Neg	Neg	82/18	78/21	10,500	13,900	0 0	0 0
R P	26	25	Neg	Neg	66/29 5	49/31	5,800	4,850	4 5	11 0
R G	45	27	30 leukocytes per cu mm	Neg	69 5/26	69/21	6,100	5,000	5 0	5 0
K P	44	35	Neg	Neg	79 5/	66/31	11,950	9,500	3 0	2 0
L S	32	46	Neg	Neg	81 5/18	64/34	10,200	7,500	0 0	1 0
M W †	48	27*	Neg	—	82/17 5	—	12,900	—	0 5	—
W C	44	39	Neg	Neg	67/25	51/34	5,700	5,500	7 0	5 5
F D	47	23	Neg	Neg	55 5/43	40/52	6,950	5,950	1 0	4 0
G G	42	26	Neg	Neg	55/41 5	40/54 5	8,300	6,300	2 5	4 0
J J	49	26	Neg	Neg	74 5/22	58/34	11,650	10,700	2 5	4 0
J P	30	28	Neg	Neg	71/21	49/31	11,750	6,300	7 0	16 5
U P	48	31	Neg	Neg	46/53	40/55	4,100	4,600	1 0	2 0
M R	34	24	Neg	Neg	70/27 5	58/41	7,850	12,150	2 5	1 0
J S	43	78	Neg	Rare RBC per cu mm	65/27 5	47 5/49 5	10,100	7,600	5 5	1 0
A S	41	21	Neg	Neg	67 5/30 5	58/35	7,550	10,650	1 5	5 0

\* Obtained during course of treatment

† Patient died

## RESULTS

All patients had a normal caloric response, audiogram, concentration non-protein-nitrogen in the blood, and urinalysis prior to starting the treatment. The hemograms were normal in all except 5 in which there was an eosinophilia greater than 4 per cent. Two patients were in the streptomycin-treated group and 3 in the dihydrostreptomycin group (table 2).

The first symptom complained of by all of the patients was soreness at the site of injection which in the majority of cases persisted throughout the treatment. In the dihydrostreptomycin-treated patients, there was a marked diminution in complaints of local soreness and pain when dihydrostreptomycin sulphate was substituted for dihydrostreptomycin hydrochloride. The dihydrostreptomycin hydrochloride was given for the first six weeks of treatment.

### *Streptomycin Sulfate-treated Group*

In the streptomycin sulfate-treated group, no significant symptoms developed until the third week of treatment.

On the fifteenth day of treatment one patient (S. M.) began to complain of severe dizziness, ataxia, visual disturbances, and had spontaneous nystagmus, all of which progressed during the next forty-eight hours. Streptomycin was discontinued on the eighteenth day, after which the symptoms rapidly disappeared. Caloric stimulation tests performed on the tenth, seventeenth, and twenty-fourth days were normal. A caloric stimulation test on the thirty-first day of treatment showed no response to ice water and all tests since that time showed no response.

Another patient (J. B.) developed symptoms on the eighteenth day of treatment lasting for approximately five days. Treatment was not discontinued at this time because the symptoms were considered to have a large subjective component and because the patient's disease seemed to respond favorably to streptomycin. The drug was finally discontinued on the twenty-third day because of increasingly severe vestibular symptoms. A caloric test on the seventeenth day of treatment, just before the onset of symptoms, was normal. Unfortunately, the patient became recalcitrant when her symptoms began and for the next two weeks refused the test. On the thirty-eighth day there was no response to ice water. Since that time weekly tests have shown no response except for a diminished response on three scattered occasions, including the last test which was four months after treatment was started (figure 1).

A third patient (D. S.) developed dizziness and ataxia on the twenty-second day of treatment and the drug was stopped five days later (twenty-seventh day). The caloric response on the twenty-fourth day was normal but there has been no response after the thirty-first day.

A fourth patient (B. W.) experienced transient dizzy sensations on the fourteenth day of treatment which were of short duration and not considered severe enough to justify cessation of treatment. She became ataxic, complained of severe dizziness, and had nausea and vomiting on the twenty-eighth day of treatment. The drug was stopped on the thirtieth day of treatment, after which the symptoms subsided. The caloric stimulation test on the thirty-first day of treatment showed a normal response.

A fifth patient (J. M.) developed symptoms on the twenty-third day of treatment consisting of dizziness, blurred vision, tinnitus, and ataxia. Spontaneous nystagmus was also noted. These symptoms increased in severity until the thirtieth day, at which time the treatment was stopped. A caloric test on the

seventeenth day was normal, but those on the twenty-fourth and thirty-first days were interpreted as showing diminished response. On the thirty-eighth day the test showed no response and all subsequent tests have yielded a similar result.

A sixth patient (I A) complained of mild dizziness on the eighteenth day of treatment but her symptoms were not sufficiently severe or characteristic to justify the diagnosis of vestibular damage due to streptomycin. Streptomycin was therefore continued. On the fifty-second day there was progression of her symptoms and a caloric stimulation test showed no response to ice water. Because of this evidence the treatment was discontinued two days later.

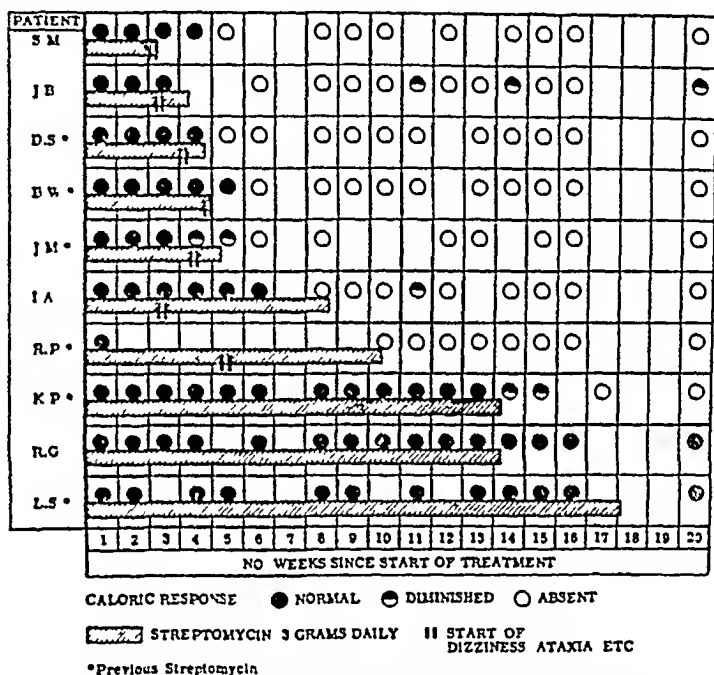


FIG 1 Relation of symptoms, caloric response and streptomycin treatment (10 patients treated with 3.0 Gm. daily)

(fifty-fourth day) This patient had normal caloric response on the twenty-fourth, thirty-first, and thirty-eighth days during all of which time she was dizzy. The dizziness and unsteadiness of gait which had persisted until the fifty-fourth day rapidly subsided after the drug was stopped. Except for a diminished caloric response on the seventy-third day, all tests since that time have shown no response.

A seventh patient (R P) had a normal caloric response at the start of treatment but was considered too ill to be retested until the sixty-sixth day of treatment when a total loss of response was demonstrated and the drug was stopped. This patient complained of dizziness in the third week of treatment persisting as long as the treatment was continued. All the caloric tests after the sixty-sixth day have shown no response.



An eighth patient (K P) experienced mild dizziness throughout the ninety days of treatment. At no time was it considered severe enough to indicate vestibular damage. The caloric response throughout treatment was normal. On the fourth and eleventh days after the cessation of treatment, some dizziness was still present and the caloric response was diminished. Eighteen days after the treatment was stopped the caloric response was absent and a follow-up test forty-six days later showed the same result.

The ninth patient (R G) was treated for the full three months, receiving a total of 270 Gm without experiencing any abnormality in caloric stimulation. Seven weeks after cessation of treatment she was still found to have normal caloric response and no specific symptoms or signs of toxicity.

The tenth patient (L S) received the full 270 Gm course of treatment and an additional 96 Gm immediately thereafter, bringing the total amount received under the study to 366 Gm. He has been completely free of signs and symptoms of toxicity up until the present date. All caloric stimulation tests up to three weeks post treatment were normal.

#### *Dihydrostreptomycin-treated Group*

One patient (M W) who had far advanced disease died after fifty-seven days of treatment without showing any toxic manifestations. Her death was attributed to pulmonary insufficiency. The remaining 9 patients in this group received ninety days of treatment. None of these showed any abnormality in the caloric stimulation test or experienced any symptoms referable to vestibular damage. When retested seven weeks after the completion of treatment, there was no evidence of vestibular damage.

Although the audiograms showed a slight increase in hearing loss in both groups of patients during the treatment and observation periods, there was no significant difference between the loss in the two groups, and what apparent difference was found can probably be ascribed to the fact that the pretreatment and post-treatment tests were done by two different examiners (table 3). In no case was there as marked a change in the audiogram as has been described by Romansky (5), and all of the patients were able to hear the spoken voice without difficulty.

One patient (J J) complained of a roaring tinnitus in the left ear, with its onset four weeks after completing the three month course of dihydrostreptomycin. Her audiogram two weeks later showed a marked loss at 8,192 cycles in the left ear, but an essentially normal curve through the rest of the audiogram. Twelve weeks after the end of treatment the tinnitus was still present and, although it affected the left ear only, the high-pitch deafness was found to involve the right ear also. There was no significant hearing loss throughout the lower frequencies in the vocal range and, although the patient complained of difficulty in hearing conversation, an interview conducted in almost whispered tone was understood readily. Otoscopic examination was negative.

One patient (J S) treated with dihydrostreptomycin showed an increase in from 13 mg per 100 cc before treatment to 78 mg per 100 cc at the end of

treatment in the blood nonprotein-nitrogen, and red blood cells were present in a catheterized specimen of urine one week after treatment. This patient left the hospital against advice and follow-up was not possible.

TABLE 3  
*Interpretation of Audiograms*  
*Per cent of "Usable Hearing" Lost During Treatment*

	BEFORE TREATMENT	AFTER ONE MONTH OF TREATMENT	SIX WEEKS AFTER CESSATION OF TREATMENT	TWELVE WEEKS AFTER CESSATION OF TREATMENT
<b>Dihydrostreptomycin Group</b>				
W C	0 0	0 0	—	—
F D	5 6	2 0	0 4	1 2
G G	0 1	0 0	—	9 4
J J	0 0	0 3	1 5	2 2
J P	0 7	1 1	—	10 7
U P	0 3	0 0	—	3 5
J S	5 1	0 1	—	6 6
A S	1 8	0 0	3 8	6 7
M R	—	0 4	0 0	0 9
M W	1 7	0 8	Died	Died
Average	1 7	0 5	1 4	3 9
<b>Streptomycin Group</b>				
I A	0 2	0 3	—	0 6
J B	0 0	0 1	—	7 4
R G	0 7	0 0	0 6	4 9
S M	47 1*	45 5*	6 5*	7 0*
J M	2 8	0 1	—	11 6
K P	8 6	6 3	—	—
R P	1 0	0 3	0 7	0 9
D S	0 5	0 7	2 8	1 3
L S	1 0	1 1	0 9	1 7
B W	3 5	6 8	2 0	5 7
Average	2 0	1 7	1 4	4 3

\* Not included in averages

There was also an eosinophilia greater than 4 per cent in 5 patients, 3 patients in the dihydrostreptomycin-treated group and 2 in the streptomycin-treated group. Only one of these patients (R P) experienced toxic symptoms (table 2).

This study was not primarily intended for comparison of clinical improvement so that no conclusion as to the clinical efficacy can be made.

#### DISCUSSION

The high incidence (80 per cent) of vestibular damage among the streptomycin-treated patients is striking when compared with the almost complete absence

of toxicity in the dihydrostreptomycin-treated group. Although this was a small study, the difference is statistically significant.

In table 1 a comparison is made between the two groups of patients as they were at the time the study was started. Six of the streptomycin group had a history of some previous streptomycin treatment, as compared with 2 in the dihydrostreptomycin group. None of these patients had been treated with more than 20 mg per Kg daily, and only 2 (one from each group) had been treated within the six-month period preceding this study. None had shown any signs or symptoms of streptomycin toxicity during or after their previous streptomycin treatment.

The disproportionate number of patients previously treated with streptomycin in the streptomycin-treated group would be grounds for challenge of the comparability of the two groups were it not for the striking difference in the incidence of toxicity found in these two groups during the study. Of the 8 patients in the streptomycin group in whom vestibular damage occurred, 7 developed definite evidence of this damage before the fifth week of treatment and before more than 100 Gm of streptomycin had been given. Four of these patients had previously been treated with varying amounts of streptomycin (30 to 150 Gm) but in none of these 4 patients did the total amount of streptomycin received, both prior to and during the study, exceed 200 Gm before vestibular damage occurred.

Two other patients in the streptomycin group had been given the drug previously. One of these has shown no measurable toxicity. The other (K P) had been given 18 Gm of streptomycin immediately prior to the study at the rate of 10 Gm daily, and showed no definite toxicity until one week after completing the 270 Gm course of treatment. He was the only example of vestibular damage in the streptomycin group resulting from more than 200 Gm of streptomycin, whereas all of the 9 patients in the dihydrostreptomycin group tolerated 270 Gm or more with no measurable vestibular damage whatsoever.

Hinshaw, *et al* (4) reported that of 14 patients treated with dihydrostreptomycin only 2 showed any evidence of vestibular damage. One of these had developed symptoms of vestibular damage from being treated with streptomycin for twelve days before dihydrostreptomycin was started. The other patient developed what was described as "mild symptoms of vestibular dysfunction" after forty-two days of treatment with 30 Gm per day. Although treatment was discontinued, subsequent caloric tests revealed "moderate hyporeactivity of the vestibular apparatus." None of the patients in this series was treated with as large a total dose of dihydrostreptomycin as the patients in our study, although one patient was treated for one hundred and twenty days. The method of testing for caloric response was not described.

Hobson, *et al* (3) treated 12 patients with dihydrostreptomycin with less striking results. Some of the drug, however, was in a relatively impure form. Seven of these patients were given 50 Gm daily for sixty-five to one hundred and ten days. Of these, 1 showed no caloric response at intervals varying from thirty-three to one hundred and fifty-two days after the beginning of treatment. One patient developed dizziness on the forty-second day of treatment but was treated 1

for seventy-five days and did not develop an abnormal caloric response until more than one hundred and two days after the start of treatment. Four patients were treated with 3.0 Gm. a day for forty to one hundred days and of these only one was reported as showing an abnormal caloric response, this being a "transient" absence of response on the thirty-second day of treatment. Presumably subsequent calorics were normal. Smaller doses of dihydrostreptomycin for shorter periods of time apparently produced no vestibular damage.

Romansky, Katz, and Glorig (5) have treated parallel groups of patients with 2.0 and 3.0 Gm. per day of dihydrostreptomycin or streptomycin and report that after three months of treatment the incidence of absent caloric response was about equal in both groups, but that the onset of this damage tended to be delayed with dihydrostreptomycin. These investigators used a modification of the Glorig and Fowler caloric stimulation tests similar to that used in the present study. The correlation between absence of caloric response and presence of characteristic symptoms was good in the present study. The team performing the tests was not aware of the symptoms and did not know which drug the patients were receiving. The technique of caloric testing was observed by one of the originators of the test on one occasion and found reliable. We believe it is safe to conclude from the reported observations that administration of a total dose of 270 Gm. of dihydrostreptomycin in ninety days has caused lower incidence of toxicity than would be expected from previously reported studies.

Of the 8 patients in this study who lost their caloric response as a result of being treated with streptomycin, 2 had normal caloric tests at the time treatment was stopped. In another, symptoms of vestibular damage appeared one week before the ninety days of treatment were completed. It was also noted that, when toxic symptoms caused the treatment to be stopped, there was still progression of the damage to a point where there was no response to the stimulation of the semicircular canals. No return of caloric response to normal was observed in any patient during the follow-up period. With the dosage of 3.0 Gm. of streptomycin a day, cessation of treatment does not appear to prevent or minimize the appearance of objective evidence of vestibular damage. None of these patients now appear to be seriously handicapped in the subsequent period of observation.

The lack of damage to the hearing apparatus among both streptomycin and dihydrostreptomycin patients is in marked contrast to the findings of Romansky, Katz, and Glorig (5). With similar doses of dihydrostreptomycin hydrochloride, approximately 20 per cent of their patients showed a marked loss of hearing which progressed several weeks after the end of treatment. In our series no such hearing loss was found, although audiograms were done for twelve weeks after the end of treatment.

In our patients the hydrochloride salt was given for only six weeks, after which the sulfate was used exclusively. Possibly the change to the sulfate forestalled the development of hearing loss, but it is not possible to assume this on the basis of the data available. Further study is needed to clarify the relative toxicities of these two salts of dihydrostreptomycin.

## SUMMARY

Ten patients were treated with streptomycin sulfate, 3.0 Gm per day for a maximum of ninety days, and 9 patients were treated with dihydrostreptomycin, 3.0 Gm per day for ninety days. All patients were observed daily for toxic manifestations, and weekly tests of caloric response were conducted. None of the patients treated with dihydrostreptomycin showed any signs or symptoms of streptomycin toxicity during the period of treatment or for seven weeks thereafter. Eight of the streptomycin-sulfate-treated patients developed symptoms of vestibular damage and subsequently lost their caloric response, even though treatment was usually stopped shortly after the onset of symptoms. The remaining 2 streptomycin-sulfate-treated patients showed no signs of toxicity in any form. The characteristic signs and symptoms of vestibular damage were always followed or accompanied by complete loss of caloric response whether treatment had been discontinued or not. No significant hearing loss was noted in either group of patients during or after treatment.

## CONCLUSIONS

1. The particular lots of dihydrostreptomycin used in this study in a dose of 3.0 Gm a day given over a period of ninety days were much less toxic to the vestibular apparatus than an equal dose of streptomycin.

2. Discontinuing treatment with 3.0 Gm doses of streptomycin because of the appearance of vestibular dysfunction will not prevent its progression.

3. All patients who had lost their response to caloric stimulation showed previous symptoms of vestibular dysfunction.

4. None of the patients showed any significant hearing loss during or after treatment.

5. Further studies are needed to clarify the effect of discontinuing treatment when smaller doses of streptomycin or toxic doses of dihydrostreptomycin are used.

6. Because of the method of selection of patients for this study, it is impossible to come to any conclusions concerning therapeutic effects.

7. Further studies should be done comparing the relative toxicity of dihydrostreptomycin hydrochloride and dihydrostreptomycin sulfate.

## SUMARIO

*Estudio Clínico de los Efectos Tóxicos de la Dihidroestreptomicina y la Estreptomicina*

Diez enfermos fueron tratados con sulfato de estreptomicina, 3.0 Gm diarios hasta un máximo de noventa días, y otros 9 tratados con dihidroestreptomicina, 3.0 Gm diarios por noventa días. Todos los pacientes fueron observados diariamente en busca de manifestaciones tóxicas ejecutando además pruebas semanales de la reacción calórica. Ninguno de los enfermos tratados con dihidroestreptomicina mostró el menor signo o síntoma de intoxicación estreptomycínica durante el período de tratamiento o por siete semanas después de haberlo

los tratados con sulfato de estreptomicina revelaron síntomas de lesión vestibular y perdieron depués su reacción calórica, aun cuando el tratamiento fué por lo general suspendido poco después de la iniciación de los síntomas. Los otros 2 tratados con sulfato de estreptomicina no revelaron signos de intoxicación en ninguna forma. Los típicos signos y síntomas de lesión vestibular fueron siempre seguidos o acompañados de pérdida total de la reacción calórica, y se abandonara o no el tratamiento. Ni en uno ni en otro grupo de enfermos notóse pérdida significativa de la audición durante el tratamiento o después.

#### CONCLUSIONS

1 Los lotes de dihidroestreptomicina usados en este estudio a dosis de 3.0 Gm diario, administrados durante un período de noventa días, fueron mucho menos tóxicos para el aparato vestibular que una dosis igual de estreptomicina.

2 La suspensión del tratamiento con dosis de 3.0 Gm de estreptomicina, debido a la aparición de disfunción vestibular, no impedirá la agravación de la última.

3 Todos los pacientes que perdieron su capacidad para reaccionar a la excitación calórica revelaron antes síntomas de disfunción vestibular.

4 Ninguno de los enfermos mostró mayor pérdida de la audición durante el tratamiento o después.

5 Necesítanse más estudios para esclarecer el efecto de la suspensión del tratamiento cuando se usan dosis más pequeñas de estreptomicina o dosis tóxicas de dihidroestreptomicina.

6 Debido al método seguido en la selección de enfermos para este estudio, resulta imposible alcanzar conclusiones relativas a efecto terapéutico.

7 Deben realizarse nuevos estudios comparando la relativa toxicidad del clorhidrato de estreptomicina y del sulfato de dihidroestreptomicina.

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greater severity over a period of several months, was common to most of the patients discussed.

*Physical examination:* Physical examination usually revealed tenderness, particularly over the right lower quadrant. Thickening of the cecum and gaseous distention of the abdomen were occasionally noted.

*Roentgenographic examination:* Roentgenographic examinations by means of barium enema were done before, during, and after the course of treatment. The procedure was repeated recently in all patients still available to determine late results. The findings varied considerably. The commonest positive finding consisted of spasticity of the colon, particularly in the cecum and ascending colon, and in some cases irregularity of the mucosa, suggesting ulceration. Shortening and contraction with deformity occurred in some. Double contrast enemas were not used.

*Proctoscopic examinations:* Proctoscopic examinations were done at intervals; usually the instrument was inserted to a point about 24 cm. above the anus.

*Bacteriologic studies:* Examination of the stools for tubercle bacilli was done in some cases but was of practically no value in verifying the diagnosis because of the fact that practically all patients in this series were discharging tubercle bacilli in the sputum. Tubercle bacilli can be found in the stools of 30 per cent of patients with pulmonary tuberculosis with no demonstrable gastrointestinal disease.

*Assignment into groups:* On the basis of the diagnostic evidence, the cases were divided into three groups. The first group consisted of 12 patients diagnosed as "verified tuberculous enterocolitis" because of symptoms, physical examination, and course, with or without roentgenographic findings compatible with the disease. In every instance, however, the diagnosis was verified by the finding of tuberculous ulcers on proctoscopy, or the finding of tuberculous lesions on biopsy of the appendix, or by post-mortem findings. The second group consisted of 10 patients diagnosed as "probable tuberculous enterocolitis" on the basis of symptoms, course, and physical examination, usually with bowel roentgenographic findings compatible with this disease. In the opinion of experienced clinicians, there was practically no doubt possible that this group had tuberculous enterocolitis. The third group of 8 patients was diagnosed as "suspect tuberculous enterocolitis" because of symptoms and physical findings suggestive of the disease before therapy. The diagnosis is open to question among the patients in the third group. It is probable that some of these had other causes for their symptoms, particularly functional bowel distress, or they may have had both functional and tuberculous disease. Cases of tuberculous peritonitis are not included in this series.

*Therapeutic regimen:* All patients were on routine sanatorium rest treatment and received a special nonirritating diet before, during, and after streptomycin treatment. Efforts were made to rule out other gastrointestinal disease by appropriate studies. Many patients had a preliminary course of antiamebic medication as a therapeutic trial. All stools were negative for bacillary dysentery, and no evidence of nonspecific ulcerative colitis was present on proctoscopic examination.

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Dosage of streptomycin varied from 0.5 Gm. in one intramuscular injection daily to 2.0 Gm. daily divided into four injections. The duration of treatment varied from forty-five days to several months. The larger dose and longer duration of treatment were used at the beginning of streptomycin treatment in 1947. The majority of the patients received the small dose and short duration of treatment which is still in use.

### *Observations*

In addition to the usual monthly re-examinations of each patient for pulmonary disease, data were collected at intervals on gastrointestinal symptoms, barium enema findings, proctoscopy, stool examinations, and resistance of the microorganisms. All drug-sensitivity tests were performed on tubercle bacilli isolated from the sputum. The follow-up observations were continued to the present time on all patients still alive.

### RESULTS

The outstanding features of each case in Groups I and II are shown in tables 1 and 2. The Group III (suspect) cases are not tabulated because of the paucity of objective findings in this group.

*Symptoms* In Group I, the "verified" group, 9 (75 per cent) patients showed marked improvement in bowel symptoms, one was unimproved, and 2 died at the end of the course of treatment. In most cases the symptoms were brought under control very quickly, sometimes within a few days, usually within a few weeks. By "marked improvement" is meant great diminution or absence of anorexia, nausea, emesis, abdominal distress, and diarrhea. Gain in weight and improvement in general condition usually followed.

In Group II (10 cases of "probable tuberculous enterocolitis") 4 patients died, 4 (40 per cent) showed marked improvement, 2 (20 per cent) showed slight improvement.

In Group III ("suspect") 4 (50 per cent) patients showed improvement and 4 showed no change.

Of all the patients who showed definite improvement of symptoms on treatment only 3 had recurrence. This was associated with progression of the patients' pulmonary disease several months after the end of treatment.

*Physical examination* In the patients who showed symptomatic improvement, there was generally less tenderness over the bowel than prior to therapy. In a number of the patients who achieved good results, there was complete absence of any abnormal tenderness in the cecal region for periods of many months after therapy.

*Roentgenographic findings* In the "verified" group, 9 patients showed definite abnormalities on barium enema prior to treatment, of these, 2 died, 5 showed evidence of improvement, and one was unchanged. The evidence of improvement noted usually consisted of lessened spasticity of the colon and less irregularity of the mucous membrane outline. Only one patient with a roentgenogram which revealed pathologic changes before therapy had normal roentgenographic findings after therapy.

In the "probable" group, 6 cases presented definite evidence of bowel abnormalities on barium enema prior to treatment, in 2 cases the barium enema was negative, and 2 patients were too ill for the examination. Barium enema after therapy revealed persistence of pathological findings but some improvement in 4 of the above 6 patients. One patient died, and one revealed progressive improvement to a normal barium enema eleven months after therapy. One patient with normal roentgenogram before therapy presented normal findings after therapy. One patient, normal before, showed contraction and deformity ten months later, associated with relapse in symptoms.

In the "suspect" group, 6 cases showed normal barium enemas before and throughout the observations, 2 revealed minimal evidence of pathology before and after therapy, with no essential change.

*Proctoscopic examination* In Group I, 9 patients had single or multiple ulcers prior to therapy, in one case the bowel appeared normal, and in 2 cases proctoscopy was not done.

In Groups II and III, all proctoscopic examinations were negative before and after therapy.

Repeat examinations after therapy revealed healing of all the ulcers except in one patient, in whom some were still present, though smaller two months later. Healing could be noted within a period of weeks. All ulcers remained healed, but in one patient two small (3 mm) new ulcers were found nine months after therapy.

*Biopsy* In 2 cases laparotomy was done for appendicitis and histologic sections revealed tuberculosis.

*Post mortems* Two patients died shortly after the end of streptomycin therapy. Post mortems revealed extensive ulcerative colitis in both cases, but no change was observed that could be attributed to streptomycin treatment. These 2 patients (M D and L T) failed to respond well to streptomycin therapy. Neither had received the drug before. Tubercle bacilli obtained from the sputum were "slightly resistant to 12.5  $\gamma$ " in one, the other had a negative culture. Symptoms were diminished in one patient while on treatment, unchanged in the other. Both patients had a rapidly progressive course to death. The failure to respond to chemotherapy must be attributed to overwhelming infection in the terminal stage of the disease. There was no evidence to suggest that healing occurred on therapy, with relapse later.

#### *Correlation of Pulmonary and Bowel Improvements in Groups I and II (22 Cases)*

In 8 patients whose chest roentgenograms showed definite improvement on streptomycin treatment, improvement of bowel symptoms was also noted. Two of these later showed progression of pulmonary disease with recurrence of bowel symptoms three and twelve months after the end of streptomycin therapy.

Of the group whose chest roentgenograms revealed no definite evidence of improvement, 6 patients died, with slight or no improvement in bowel symptoms, 5 patients had ulcers heal and experienced marked improvement in bowel

TABLE 1  
Group I Verified Cases of Tuberculous Enterocolitis

CASE	TREATMENT	SYMPTOMS		PHYS EXAM (abd)		PROCTOSCOPIC		BARIUM ENEMA		END RESULT	PULMONARY ROENTGENOGRAM
		Before	After	Before	After	Before	After	Before	After		
1 J S M N 30 years FAB—Positive	9/11/48 60 days 0.5 Gm Sens SR 100 γ	Appetite poor Distress Diarrhea	Appetite good No pain BM normal	Tender ++	None	12 ulcers 2 to 5 mm diameter	Completely healed	Narrow spastic cecum and transverse colon	Unchanged	6 months after treatment patient feels improved but has extensive pulmonary tuberculosis + 34 pounds	No change 3 months after treatment
2 M D F W 18 years FAB—Positive	9/8/47 60 days 1.0 Gm Sens No rept	Anorexia N&L++ Pain Diarrhea	Same	Tender	Same	Not done Too ill	Too ill	Spasm of cecum	Not repeated	Died after 60 days of treatment PM revealed extensive ulcer throughout colon	Progressive disease
3 L T M N 31 years FAC—Positive	9/3/48 60 days 0.5 Gm Sens SR 12.5 γ	Anorexia N&L++ Pain++ Diarrhea	Improved while on therapy Regressed thereafter	Tender	Same	1 ulcer 4 to 5 mm	Not repeated Too ill	Spasm of cecum	Not repeated	Died one month after end of therapy PM revealed extensive ulcer throughout colon	No change after 60 days of therapy
4 H W F W 32 years FAB—Positive	9/3/48 120 days 0.5 Gm Sens Culture negative	Pain Diarrhea Appendectomy revealed TB	Appetite good N&L none No pain BM 1 x day	Tender	None	Normal	Normal	Normal	Normal	Asymptomatic Thoracic coplasty done after streptomycin therapy + 3 pounds	Moderate clearing on therapy followed by thoracic coplasty
5 J T F W 32 years FAB—Positive	7/4/48 120 days 0.5 Gm Sens SR 100 γ	Cramps Diarrhea 3 to 5 x day	Appetite fair N&L none Pain 0 BM 1 x day	Slight tenderness	2 ulcers 3 mm	Healed with scarring New ulcers present 9 months later	Healed	Cecum irregular and spastic	Normal	March 1949 minimal bowel symptoms Thoracic coplasty being done + 30 pounds	Progressive disease
6 B T F N 23 years FAB—Positive	8/3/48 120 days 0.5 Gm Sens SR 100 γ	Cramps Diarrhea 2 to 3 x day	Appetite good N&E none Pain 0 BM 1 to 2 x day	Tender	Several small ulcers	Healed	Normal	Normal	Normal	Bowel symptoms absent 60 days after therapy General condition poor + 10 pounds	Pulmonary disease progressing

7 D H I N 21 years FAB—Positive	9/30/48 90 days 0.5 Gm Sens Culture negative	Cramps Diarrhea 10 to 12 x day	Appetite fair N&D none Pain O BM 12 x day Occasional diarrhea	Ten- der	Normal	1 ulcer 4 mm	Healed	Spasm of as- cending colon	March 1949 Less spasm	Symptoms improved in 2 weeks + 10 pounds	No change in 90 days
8 A A M W 35 years FAB—Positive	9/17/47 45 days 1.2 Gm Sens No rept	Anorexia N&D Cramps Occasional diarrhea	Appetite good N&D none Pain O BM 1 x day	Ten- der mass in RLQ	Normal	Normal	Normal	Normal	Normal	Tuberculous appendix removed 18 mos after therapy patient working Feels well	No pulmonary lesions seen be- cause of prior thoracoplasty
9 S M T I N 21 years FAB—Positive	12/1/48 120 days 0.5 Gm Sens SR 100 γ	Appetite poor N&D Pain Lost 14 pounds	Appetite good N&D none Pain O BM 1 x day	Ten- der	Ulcers 2 to 10 mm diameter	Healed	Healed	Spasm and irreg of cecum	Im- proved	Bowel asymptoma greatly improved General condition not improved	Progressive dis- ease
10 J F M W 37 years FAB—Positive	11/20/48 120 days 0.5 Gm Sens SR 100 γ	Anorexia Cramps Diarrhea Wt loss Fever	Anorexia N&D++ Pain++ BM 2 x day Wt loss Fever	Ten- der	1 ulcer 8 mm	Healed	Healed	Irreg and spasm of cecum	Marked im- provement	Bed patient Failing	Slight clearing
11 E H F N 20 years FAB—Positive	1/10/49 120 days 0.5 Gm Sens SR 10 γ	Anorexia N&D occurs Cramps Diarrhea 4 to 5 x day	Appetite good N&D none Pain O BM 1 x day	Tender Losing wt	Ulcers 2 to 5 mm	Mostly healed, a few healing March 1949	Mostly healed, a few healing March 1949	Deformity of cecum	Consid- erable im- provement	Diarrhea stopped in 2 weeks + 5 lbs in 1 month Thoracoplasty done while on therapy	Cannot evaluate because of thoracoplasty
12 W N M W 43 years FAB—Positive	5/13/48 60 days 0.5 Gm Sens Culture negative	Anorexia Cramps Diarrhea 3 to 4 x day	Appetite good N&D none Cramps O	Ten- der losing wt	Several small and one large ul- cer	Healed	Healed	Spasm and deformity of cecum with ul- ceration	No spasm	Bowel asymptomatic General condition stationary + 9 pounds	Marked clearing

N & E Nausea and Emesis    Sens    Sensitivity bacillus    SR    Slight Resistance    CR    Complete Resistance    PNX    Pneumothorax

TABLE 2  
Group II Probable Cases of Tuberculous Enterocolitis

CASE	TREATMENT	SYMPTOMS		PHYS EXAM (mm)		PROCTOSCOPIC		BARIUM ENEMA		FIND RESULT	PULMONARY ROENTGENOGRAM
		Before	After	Before	After	Before	After	Before	After		
13 W B M N 40 years FAC-Positive	9/3/48 120 days 0.5 Gm Sens Culture negative (10/1/48) SR 12.5 γ	Anorexia Pain Diarrhea 3 to 4 x day	Slight im provement Died	Tender Dis- tended	Tender Dis- tended	Negative to 24 cm Fistula in ano	Not re-ex- amined Died	Nothing de- fect in cecum	Marked im- provement 2/3/49	Died March 1949 Slight improvement in bowel symptoms	Progressive dis- case
14 C B T W 46 years FAC-Positive	5/28/48 60 days 0.5 Gm Sens CR 100 γ	Anorexia Nausea Pain Diarrhea 8 to 10 x day	Slight im- provement	Tender	Tender	Too ill for examination	Died	Not done because too ill	Died	Died March 1949 Slight improvement in bowel symptoms	No change
15 A D F N 22 years FAC-Positive	10/4/47 71 days 1.0 Gm Sens No rept	Anorexia Nausea Emesis Pain Diarrhea	No im- provement	Tender Dis- tended	Same	Too ill for examination	Died	Not done Too ill	Died	Died February 1948 No improvement in bowel symptoms	No change
16 C K T W 43 years FAC-Positive	3/4/47 60 days 1.2 Gm 11/24/47 40 days 0.5 Gm Sens SR 100 γ (11/4/47)	Anorexia Occasional nausea Pain RLQ	Slight im- provement with re- currence later	Cecum pal- pable	Tender RLQ	Negative to 24 cm	Negative	Very marked spasm, cecum and asc colon Rough mu- cousal pat- tern	March 1949 No formed but not spas- tic	Improvement on treatment not main- tained following slowly	Moderate clearing followed in 1 year by pro- gression

17 G K F W 23 years FAB—Positive	5/15/47 195 days 10 Gm Sens No rept	Anorexia Pain RLQ	Improved No Pain	Ten der RLQ	Marked ten der ness RLQ	Negative to 24 cm	Negative	Peristent spasm through out colon, especially cecum	Jan uary 1948 Spasitic colon June 1948 Nor mal March 1949 Nor mal	Bowel symptoms mini mal 22 months after therapy Chest con dition stationary	Considerable clearing
18 J McV M W 35 years FAB—Positive	4/24/47 72 days 20 Gm 7/9/47 134 days 15 Gm Sens No rept	Anorexia Nausea Emesis Pain Diarrhea	Appetite good No nausea, emesis or diarrhea	Ten der	Slight ten der ness RLQ	Negative	Negative	Very marked spasm of ascending colon Mucosa irregular	March 1940 Moder ate im provement	March 1949 Gained 50 lbs Late every thing General condition good Thomeoplasty done September 1948	Improved
19 W S F W 37 years FAB—Positive	7/6/48 65 days 05 Gm Sens SR 100 γ	Anorexia Discomfort Diarrhea	Improved but re curred	Ten der	Ten der, Dis tended	Negative	Negative	Normal	Nor mal March 1940	Temporary improve ment March 1949 Anorexia, occasional emesis BM 1 to 3 x day + 8 pounds Hus amyloidosis Tailing	Improved
20 H S F W 38 years FAB—Positive	1/6/48 142 days 05 Gm Sens No rept	Anorexia Emesis Pain Diarrhea	No im prove ment	Ten der	Ten der	Negative	Died	Ulceration of proxi mal one half of colon	Died	Died May 1948	Progression of dis ease
21 S S F W 25 years FAB—Positive	6/18/48 134 days 10 Gm Pre ther apy Sens SR 15 γ	Nausea Emesis Diarrhea	Spectacu lar im prove ment in 5 days	Ten der	No ten der ness on deep pres sure	Negative	Negative	Marked shorten ing, ir regular, and spasm of terminal ileum, asc es and trans colon	March 1949 Slight im prove ment	10 months after ther apy patient is at home Appetite good, eats every thing except fruits + 33 pounds BM 1 x day, formed	Marked clearing Pnx right and lyss Extrapi pnx left done recently

TABLE 2—Concluded

CASE	TREATMENT	SYMPTOMS		PHYS EXAM (AND )		PROCTOSCOPIC		BARIUM PHENEA		END RESULT	PULMONARY ROENTGENOGRAM
		Before	After	Before	After	Before	After	Before	After		
22 L W T W 23 years TAB—Positive	5/10/48 121 days 0.5 Gm Sens CR 100 γ (October 1948)	Anorexia Nausea Pain Diarrhea	Improved for 7 months then re lapsed 3 months after therapy	Tender RLQ cecum palp	Tender RLQ	Negative	10 months after therapy ulcers noted in rectum	Normal months	10 months after therapy and control and form cecum and asc colon	3/49—Anorexia, nau sea, pain, diarrhea 2 to 3 x day Lost 16 pounds Early im provement not main tained	No improvement

symptoms, and one patient had bowel symptom improvement with recurrence in seven months

In 2 patients the presence of a thoracoplasty, one done before streptomycin treatment and one after, made evaluation of the pulmonary response difficult. In both cases marked improvement of bowel symptoms occurred.

The best results were obtained in those patients in whom collapse therapy caused the "conversion" of the sputum. Four such patients (3 thoracoplasties and one pneumothorax with lysis) remained asymptomatic three months, nine months, ten months, and eighteen months, respectively, after beginning of streptomycin treatment. Two are at home, one is working (Case 8).

#### *Correlation of Barium Enema with Streptomycin Treatment*

Improvement in symptoms was much more marked than improvement in the roentgenographic appearance of the bowel. In patients whose films showed little or no change, it was common to find marked to complete disappearance of symptoms. Improvement, when present in the roentgenogram, usually consisted only of diminution of spasm. All patients who showed improvement roentgenographically also improved symptomatically. Return of an abnormal roentgenogram of the bowel to normal was rare, but was noted in one patient over a period of eleven months. Symptoms in this patient improved rapidly on treatment.

#### *Dose and Duration*

The small number of patients allows of no significant statistical analysis of the effectiveness of the various streptomycin regimens. However, the 0.5 Gm., sixty-day course of treatment apparently produced good results in suppressing symptoms and in the duration of this effect. The larger doses and longer courses gave no definite evidence of better results.

#### *Drug Resistance of Microorganisms*

Values for the drug resistance of the tubercle bacilli obtained from the sputum at the end of therapy in each case (where available) are indicated in tables 1 and 2. The designation S means sensitive, VSR, very slightly resistant, SR, slightly resistant, and CR, completely resistant. The organisms were cultured on solid medium with 10  $\gamma$ , 10 $\gamma$ , and 100 $\gamma$  of streptomycin per cc. Data are insufficient to determine the effect of resistance on the further clinical course of the enteritis.

#### DISCUSSION

Prior to the widespread use of collapse therapy, tuberculous enterocolitis was very common, and large numbers of examples were always present in this institution. Collapse therapy procedures have cut down the incidence very markedly in recent years. After the use of streptomycin on a large scale, the incidence was reduced still more, possibly because this complication was prevented either by the drug *per se*, or by the fact that collapse therapy could be used in more patients than before. As a result, the number of cases of tuberculous enteritis



seen recently is very small, and it occurs mostly in patients who already have it when admitted

It is evident that streptomycin is a most effective drug in the treatment of tuberculous enterocolitis. It usually controls the symptoms quickly, often dramatically. Most patients maintain this symptomatic relief over long periods of time, although several showed relapse in a few months. The latter were patients with progressive pulmonary lesions and sputum positive for tubercle bacilli. Some of the patients seem to remain almost asymptomatic in spite of little or no improvement in the chest roentgenogram or sputum status. In those patients whose disease was progressing rapidly toward a fatal termination, the streptomycin caused little or no improvement in symptoms. The use of narcotics in such patients to control cough, et cetera, tended to cover up the gastrointestinal symptoms, making it difficult to evaluate the effectiveness of streptomycin. In general, streptomycin therapy resulted in rapid disappearance or diminution of anorexia, nausea, emesis, abdominal discomfort, and diarrhea. Often patients became asymptomatic with good appetite and one formed bowel movement daily. They were able to eat almost all foods instead of being restricted to a special bland diet as before. Many were able to eat all the common foods except raw fruits after completion of therapy.

Prior to therapy, the abdomen, and particularly the cecal region, was tender on palpation. After therapy, this sign improved and in some of the patients seemed to disappear. Deep palpation and heavy pressure over the cecum caused no pain in some of the patients examined over a period of months after therapy.

The degree of improvement noted on roentgenographic examination seems slight in comparison with the improvement in symptoms. Although spasm usually disappeared, deformity in the cecal region remained even in the presence of no symptoms and apparently normal bowel function. It may be assumed that superficial ulceration healed and remained healed, as borne out by the clearing of the rectal ulcers. The persistence of deformity suggests deep scarring, but proof of this is still lacking.

Only 2 of the 6 patients who died came to autopsy. The bowel findings of extensive ulceration, worse in the terminal ileum, cecum, and ascending colon, appeared identical with those not treated with streptomycin. These 2 patients had been extremely ill when admitted to the sanatorium and therapy had very slight effect. In one patient diarrhea continued unchecked to the time of death. In the other patient, symptoms improved while on therapy but regressed rapidly after discontinuance, death followed in one month.

No opportunity has presented itself to study the autopsy findings in a patient who had good results from streptomycin therapy of a proved tuberculous ulcerative colitis. It would be of considerable interest to note the anatomical results.

In most cases symptoms of both bowel and pulmonary disease improved together. In a considerable number of cases, however, the improvement of bowel symptoms and objective findings was much greater than the improvement to be noted in the chest roentgenogram. It was relatively easy to obtain bowel improvement with streptomycin, but unusual among these patients to see corre-

spondingly marked objective improvement in the pulmonary picture. It seems to be much more difficult to influence pulmonary than bowel tuberculosis. Whether this difficulty is caused by the relative accessibility of the bowel lesions to the drug by way of the blood stream, or simply reflects the more massive involvement in the lungs, is not evident.

Some of the patients in this series were admitted to the sanatorium with evidence of severe bowel tuberculosis and advanced pulmonary lesions permitting of no collapse therapy. In such patients, as would be anticipated, streptomycin therapy is mainly for symptomatic relief and should be started at once. However, in patients whose general condition is better and who may become candidates for collapse therapy, the timing of streptomycin therapy becomes a matter of importance. From the present experience it would appear advisable to proceed with surgical collapse where indicated, using streptomycin to control the bowel symptoms, in the expectation that a good result will be achieved if sputum "conversion to negative" follows the surgery. In patients being prepared for pulmonary resection it is important to use streptomycin at the proper time. To dissipate its usefulness in treating minor bowel symptoms long before surgery would be unwise.

It is remarkable that reinfection of the bowel mucosa appears to be uncommon after the end of therapy. In most patients, improvement has been maintained over a number of months in spite of sputum positive for tubercle bacilli which would be expected to cause new ulcerations in the bowel. It is not clear whether this failure to reinfect the bowel is due to a diminution in the number of bacilli traversing the bowel after therapy or to some qualitative change in the bacilli. Are resistant strains less likely to cause mucosal lesions, or does the general improvement in the patient's resistance after therapy prevent reinfection? It is evident that the answers to these questions must await a more complete understanding of the mechanism of action of streptomycin.

#### SUMMARY AND CONCLUSIONS

Studies of 30 patients with tuberculous enterocolitis treated with streptomycin are reported. All had associated pulmonary tuberculosis. Diagnostic criteria, roentgenographic findings, proctoscopic findings, and end results are detailed. Of 12 cases with a "verified" diagnosis, 9 showed marked improvement after treatment with streptomycin. Of all 30 cases, 19 showed improvement. Clinical improvement was usually rapid, often dramatic, and frequently maintained even when a relapse of the pulmonary disease occurred. In 9 cases, rectal ulcers disappeared in 8 immediately after treatment. Change in the status of the roentgenographic findings during treatment did not generally occur.

#### SUMARIO Y CONCLUSIONES

##### *Estreptomycinoterapia de la Enterocolitis Tuberculosa*

Estos estudios comprenden 30 enfermos con enterocolitis tuberculosa tratados con estreptomicina. En todos había tuberculosis pulmonar. Exponemos el estudio de diagnóstico, los hallazgos proctoscópicos radiográficos y los resultados ter.

minales De 12 casos con diagnóstico "comprobado," 9 revelaron decidida mejoría después del tratamiento con estreptomycin. Del total de 30 casos, 19 mejoraron. La mejoría clínica fué por lo general rápida, a menudo dramática, y mantenida frecuentemente a pesar de la recaída de la afección pulmonar. De 9 casos, en 8 las úlceras rectales desaparecieron inmediatamente después del tratamiento. En general, no se alteraron los hallazgos roentgenográficos durante el tratamiento.

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# RASMUSSEN'S ANEURYSMS AND FATAL HEMORRHAGE IN PULMONARY TUBERCULOSIS<sup>1</sup> <sup>2</sup>

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## INTRODUCTION

One of the most dramatic complications of pulmonary disease is massive hemorrhage. This has been associated, in the minds of most physicians, with pulmonary tuberculosis, and the various aspects of this syndrome have interested many since the early writings of Laennec (1) in 1827. It remained for Fearn (2), however, in 1841 to describe for the first time in some detail the source of a hemorrhage in a patient dying of cavitary pulmonary tuberculosis. He recorded his observations of a ruptured aneurysm within a tuberculous cavity in a patient who died of multiple recurrent pulmonary hemorrhages. The greatest contribution to the consideration of the aneurysmal source of these hemorrhages may be found in the careful and detailed anatomical studies of Rasmussen (3) of Copenhagen in 11 cases published in 1868 and 1869. He described in each of these 11 cases a pulmonary vessel passing through the wall of a tuberculous pulmonary cavity with an aneurysmic dilatation of this vessel into the cavity.

More recently attention has been directed to this subject in papers by Bogen (4), who states that hemorrhage in pulmonary tuberculosis is almost always from a pulmonary artery, and by Auerbach (5), who describes a series of 45 such pulmonary arterial aneurysms in tuberculous patients dying of pulmonary hemorrhage. A variety of other hypotheses have been developed to account for pulmonary hemorrhage in tuberculous patients. Among these are deficiency of the coagulability of the blood (6), increased permeability of the vessel walls (7), and erosion of pulmonary vessels by enlarged tracheobronchial lymph nodes (8 and 9). This last condition accounts for relatively few cases of hemorrhage in pulmonary tuberculosis, and the exact status of the other conditions has not been clarified satisfactorily. Although most large hemorrhages resulting from rupture of a pulmonic arterial aneurysm occur in cases of pulmonary tuberculosis with cavitation, some occur in patients with primary or metastatic lung neoplasms, bronchiectasis, lung abscess, or other acute or chronic lung inflammations (10).

## MATERIAL

From 667 autopsies performed at Dunham Hospital of Hamilton County during the ten-year period 1938-1947, 56 cases were selected in which the patient had either died following a massive pulmonary hemorrhage, or in which an un-

<sup>1</sup> From the Percy Shields Laboratory, Dunham Hospital of Hamilton County, Cincinnati 5, Ohio.

<sup>2</sup> Presented in part at the 1948 session of the Mississippi Valley Conference on Tuberculosis.

ruptured Rasmussen's aneurysm was discovered at autopsy. Forty-nine of these 56 patients died following a massive pulmonary hemorrhage and are the basis for the clinical observations in this study. These 49 cases, with an additional 7 cases in which hemorrhage did not occur but an unruptured aneurysm of a pulmonic artery was discovered as an incidental finding at autopsy, comprise the 56 cases studied for the gross pathological data. Of the 49 patients who died following a massive pulmonary hemorrhage, a Rasmussen's aneurysm was demonstrated in only 29. It is believed, however, that the source of hemorrhage in all of these 49 cases was from such an aneurysm, for Rasmussen stated that he was able to find the source of bleeding in every case after his attention was once directed to the occurrence of these aneurysms. The writers' experience lends some support to this opinion that the more diligent the search, the higher the rate of discovery. Since 1943, when interest in this problem was stimulated at Dunham Hospital, 21 of these aneurysms were found in 26 patients who died as the result of massive pulmonary hemorrhage, while prior to this date only 8 such aneurysms were found in 23 hemorrhage cases. Also only 2 unruptured Rasmussen's aneurysms were found in cases as an incidental finding prior to 1943, whereas 5 have been disclosed since that time.

To a certain extent, the method of preserving and dissecting the lungs as routinely done in this hospital may account for failure to demonstrate the source of some of these hemorrhages. Whenever possible, the lungs and trachea are removed intact from the thorax. The lungs are then inflated with air so that a post-mortem roentgenogram of the lungs alone can be made. The lungs are then distended with 10 per cent formalin until the solution begins to ooze from the pleural surfaces. As will be further demonstrated in the pathological discussion, some of these aneurysms are thin-walled and empty. It is probable that the marked increase in the intracavitary pressure during these procedures may so collapse the aneurysmal sac that it cannot be readily recognized.

#### INCIDENCE AND ETIOLOGICAL FACTORS

Forty-nine (7.2 per cent) of the 667 patients upon whom autopsy was performed in a ten-year period died as the result of pulmonary hemorrhage. The incidence by sex and color is shown in table 1.

The average age at death for patients dying as the result of hemorrhage is compared with the average age at death for the entire autopsy series in this same period of time in table 2. The ranges of ages of those who died as a result of hemorrhage are as follows: white males 34 to 68 years, Negro males, 22 to 69 years, white females, 19 to 54 years, Negro females, 15 to 45 years. The greatest number of hemorrhages which were fatal occurred between the ages of 30 and 59. No deaths as a result of pulmonary hemorrhage occurred under the age of 21 in males, while in females 4 of the 14 died at 20 years of age or under. In Negro males, there was a ten-year difference between the mean age of the general autopsy population and that of the patients who died as a result of pulmonary hemorrhage, the latter patients dying on the average at an older age. In the other categories, there was no essential difference between the two groups.

*Duration of disease* To gain some idea of the relative duration of the disease in patients with massive pulmonary hemorrhage, the average duration of symptoms in months of the various color and sex groups was compared with a control series consisting of 100 consecutive fatal cases of pulmonary tuberculosis which was broken down into similar categories. The results of this comparison are shown in table 3. The average duration of disease for white females was actually 71.7

TABLE 1  
*Color and Sex Incidence of Fatal Hemorrhage*  
1938-1947

	FATAL HEMORRHAGE	ALL AUTOPSIES	PER CENT
White Male	21	256	8
Negro male	13	198	6.6
White female	8	96	8
Negro female	7	117	6
Total	49	667	7.2

TABLE 2  
*Average Age At Death*

	FATAL HEMORRHAGE	ALL AUTOPSIES
White male	49.80	48.90
Negro male	42.93	30.40
White female	33.10	35.40
Negro female	26.86	28.00

TABLE 3  
*Average Duration of Symptoms in Months*

	HEMORRHAGE SERIES	CONTROL SERIES
White male	30.25	21.30
Negro male	13.93	14.48
White female	52.50	38.30
Negro female	15.30	10.20

months. In this series, however, was one patient who had had clinically active tuberculosis for twenty-five consecutive years before her death. Since this case weights the average unduly, the average of the remaining cases, 52.5 months, is thought to be more representative of the entire group. In the white race, the duration of disease is about eight to twelve months longer in the group that develops an aneurysm and dies as the result of hemorrhage than in the average case that dies of pulmonary tuberculosis. In Negro males, there is apparently no significant difference in the duration of disease in patients dying of tuberculosis,

whether the complication of aneurysm does or does not arise during the course of the illness. The small number of cases in the series of Negro females, 7, precludes any valid statistical conclusions. There is considerable difference in the duration of the disease when the white patients are compared with the Negro patients. The duration is two to three times longer in the white persons, both in the hemorrhage series and in the average of the autopsy series. This pattern follows the general trend of the difference of the disease in the two racial groups. Similar trends are obtained when the average period of hospitalization of the patients studied here is considered.

TABLE 4  
*Duration of Symptoms in Months*

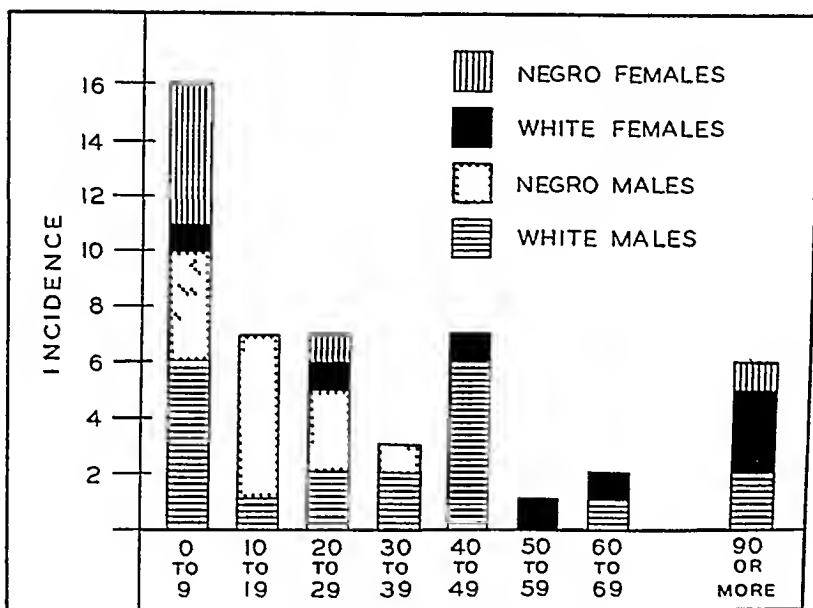


Table 4 presents a graph of the incidence of death in the hemorrhage series as compared with the duration of clinical disease in ten-month periods. In 16 of the 49 cases symptoms considered to be of pulmonary tuberculous origin had been present for nine months or less, while 33, or more than two-thirds of the patients had had similar symptoms for more than ten months. Twenty-six of this latter group had had the onset of their pulmonary tuberculosis at least twenty months before death.

Further evidence of chronicity is found in the fact that in about one-half the cases in this series bilateral and predominantly fibrocaseous tuberculosis was demonstrable in the admission roentgenograms. In 4 of these cases silicosis was also present. In 10 cases the disease was bilateral and predominantly exudative at the time of admission, and in 14 it was unilateral and exudative. The presence of cavity was detected in every case except 2, and in these, although it was not detected clinically or roentgenologically, it was found at autopsy.

*Role of syphilis* Since the presence of aneurysms frequently brings up the question of syphilis, this factor was investigated by comparing the incidence of positive serologic tests for syphilis (Hinton and Kahn) in the hemorrhage series with the incidence of positive reactions in all patients coming to autopsy during three consecutive years. In the series of patients dying as a result of massive pulmonary hemorrhage and in those in whom an aneurysm was discovered as an incidental finding at autopsy, the serologic tests for syphilis were positive in 21.8 per cent. In those with a positive reaction, an aneurysm was found in 7 and was not found in 5. In the unselected group from the general autopsy series, the serologic tests for syphilis were positive in 37 of the 175 cases, or in 21.14 per cent. This figure is practically the same as that found for the incidence in the group studied here.

TABLE 5  
*Hemorrhage prior to Fatal Hemorrhage*

None	26
One	7
Multiple	16
1 to 8 years previously	11
4 to 12 months previously	7
Less than 4 months previously	5

#### DEATH FOLLOWING HEMORRHAGE

Of the 49 patients who died as the result of massive pulmonary hemorrhage, 26, or more than one-half, had no such hemorrhage prior to the one which terminated in death (table 5). Seven patients had one previous hemorrhage, while 16 experienced multiple hemorrhages prior to the fatal one. Of the latter 23 cases, bleeding from the lungs had occurred between one and eight years prior to death in 11, between four and twelve months in an additional 7, while in 5, less than four months elapsed between the time of the first hemorrhage and the time of death.

Of the 49 patients who died as the result of pulmonary hemorrhage, 36 died immediately following this hemorrhage. This latter group includes one case in which the patient survived in a state of shock for a period of eight hours following an isolated hemorrhage. Of this group of 36 cases, 26 had no previous hemorrhage, and death appeared to be due to either blood loss or suffocation. In 3 of these 26, there was no external evidence of hemorrhage at the time of death but evidence of massive bleeding was found at necropsy. Rasmussen (3) commented on the occurrence of such an occult fatal hemorrhage. Others, writing on this subject, have failed to mention either the possibility or the finding of such cases of occult fatal pulmonary hemorrhages. In 10 of the 36 cases there had been previous hemorrhage over a period varying from three days to three months before the massive hemorrhage which was immediately fatal. Death in these 10 cases also appeared to be due primarily to blood loss or to suffocation but in a



few, spreading disease as a result of the previous hemorrhages may have been a factor. In 5 cases in which a massive blood loss in the last few hours of life did not occur there were repeated hemorrhages over a period of several days to one year before death. The mode of death in these cases appeared to be due in part to spread of tuberculosis and in part to blood loss. In 8 cases, death followed a single hemorrhage after an interval of four to fourteen days. In these, death was apparently due to spread of an acute tuberculous pneumonia as the result of the hemorrhage. This acute pneumonia may possibly have been on an allergic basis as described by Austrian and Willis (11) who observed the development of "cottony" shadows, roentgenologically, and foci of acute tuberculous pneumonia, pathologically, in the lungs of sensitized rabbits that received intratracheal injections of a mixture of blood and tubercle bacilli. Although in the majority of cases blood loss and obstruction to the trachea and bronchi appeared to be chief factors in the cause of death, in about 25 per cent the development of an acute tuberculous pneumonia may have been the immediate cause of death. Some idea of the unexpectedness of death can be gained from noting that, of the 49 patients who died as a result of massive hemorrhage, 28, or over one-half, were considered well-nourished at the time of death, a state of nutrition unusual in the average patient dying of pulmonary tuberculosis.

#### PATHOLOGY

A general survey of the lung sections in all 56 cases, including fatalities as a result of hemorrhage as well as cases in which an unruptured aneurysm was found, emphasizes the fact that these aneurysms and the resultant massive hemorrhages tend to occur in the more chronic forms of tuberculosis. Lesions of a fibro-caseous type were described in virtually every protocol of the lung dissection. The sections of the lungs were surveyed, with special attention being directed to those cases in which clinical symptoms referable to tuberculosis had been present for less than ten months. In every case in the entire series, conspicuous foci of pulmonary fibrosis due to tuberculosis were found. Frequently such fibroid or fibrocaseous foci were surrounded by large zones of caseation or monocytic tuberculous pneumonia. In those cases in which the aneurysm was found, such fibrosis was seen in microscopic sections adjacent to the artery of origin of the aneurysm in every instance but one. Microscopically, this one aneurysm did not appear different than the others in the series except for the absence of fibrosis due to tuberculosis around the vessel at the point of origin of the sac. Even in this case, however, with a clinical duration of only four months, numerous fibrocaseous foci were found scattered throughout the extensive masses of caseous and monocytic tuberculous pneumonia (figures 1 and 2).

FIG 1 (Left) Sagittal section of right lung. A Rasmussen's aneurysm is seen on the posterior aspect of the cavity in the base of the lower lobe. Bronchiectasis and the coarse honey pattern of diffuse emphysema are apparent.

FIG 2 (Right) Enlarged view of aneurysm shown in figure 1. Note the tangential course of the vessel of origin to the wall of the cavity. The thickness of the fibrotic wall of the cavity is especially apparent in the basal portion.

Fig 1

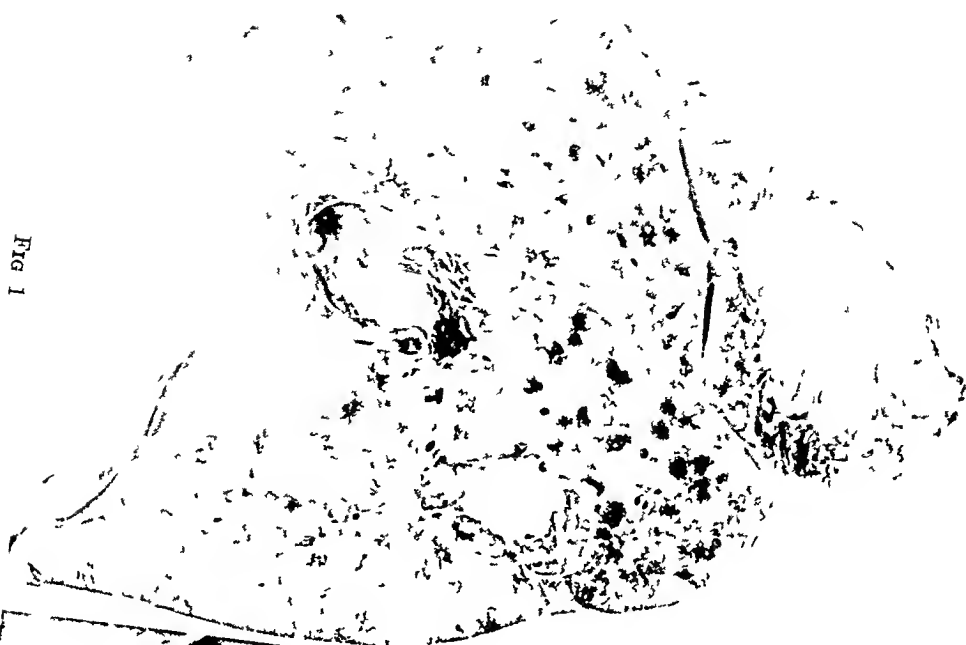
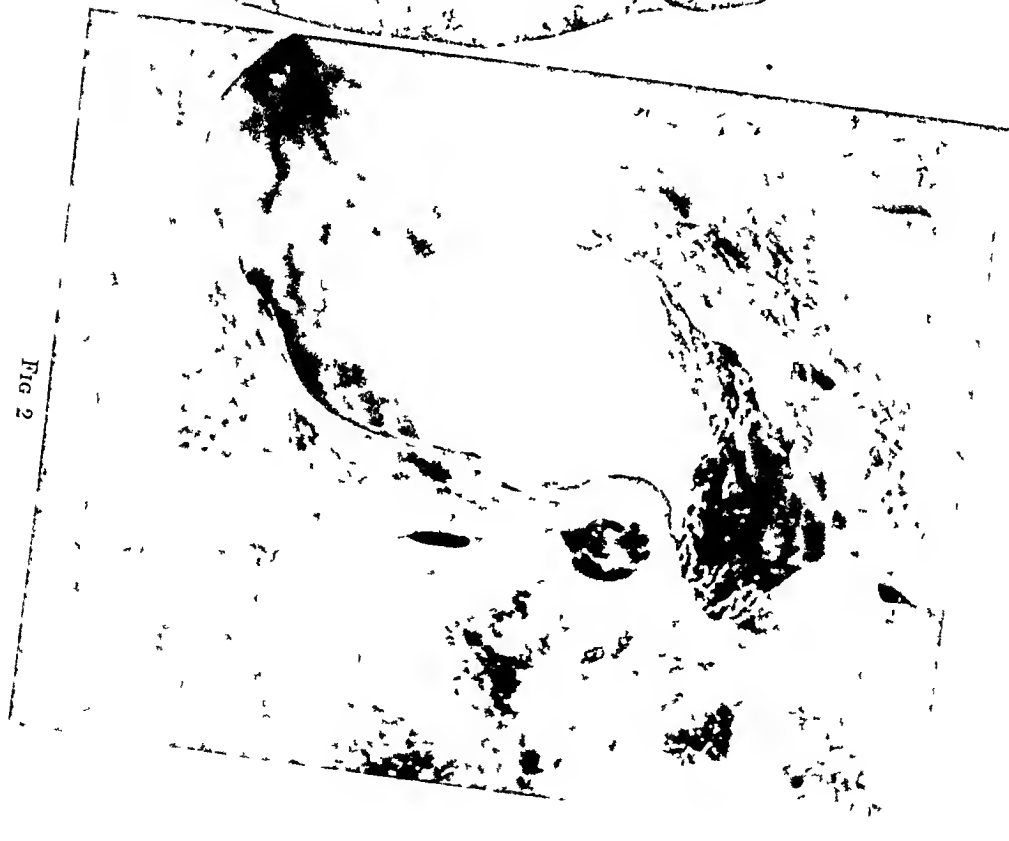


Fig 2



Other changes observed histologically were interpreted as indicative of chronic pulmonary disease. Bronchiectasis, most severe in the apical portions of the lungs, was frequently seen. These same zones were also the site of the more marked fibrosis. In addition to dilatation of the bronchi and erosion of the bronchial cartilaginous plates, focal squamous metaplasia of the bronchial epithelium was encountered with moderate frequency. Compensatory emphysema frequently seen was usually more marked in the fibrotic parts of the lungs in association with the bronchiectasis, while within the fibrous foci atelectatic alveoli lined with cuboidal cells were common.

Cavity formation was found in every case in this series at autopsy. The cavity containing the aneurysm varied in size from a minimum of 5 mm. to a maximum of 7 cm. in diameter. There was no correlation between the size of the cavity and the incidence of aneurysm formation.

Rasmussen (3) found aneurysms occurred with approximately equal frequency on each side. Auerbach (5) found that aneurysms occurred more frequently in the left lung (26 cases) than in the right lung (19 cases). In this series, single aneurysms were found fourteen times in each lung, while in 6 cases the site of the aneurysm was not recorded. In the other 2 cases aneurysms were found bilaterally, in each, the aneurysm on the right was unruptured while the one on the left was ruptured.

In 21 cases where the site of the aneurysm within the cavity was clearly described, about one-half were found on the medial wall, while the others were located with about equal frequency on the other walls except that none was found on the lateral wall of a cavity.

*Intra-arterial injection of radio-opaque material.* Using Hill's radio-opaque bismuth suspension (12), arterial injections of 9 sets of lungs were done using the technique described by Wood and Miller (13). In two instances the bronchial arteries were injected. An aneurysm was found in one case and not in the other. No reference was made to the presence or absence of the contrast medium in a cavity, lumen, in a cavity wall or in the aneurysmal sac in the case in which the aneurysm was discovered. In the other case the prosector stated that the injection medium was absent within the cavities and that it was not seen in any of the vessels in the cavity walls. The pulmonary arteries of another case were injected with the contrast medium. Gross dissection revealed the presence of an aneurysm but no contrast medium was seen grossly in the lumen of the cavity or the sac, in spite of the fact that the lumen of the vessel of origin was one mm. in diameter. In 6 other cases post-mortem arterial injections of vessels supplying the lungs were done but the protocols fail to mention which vessels were injected. In 3 of these cases an aneurysm was found, while in the other 3 an aneurysm was not identified. Slides of these lungs indicate that post-mortem injection of the pulmonary arteries had been done in 4 of these cases. In one, injection material was found in the lumen of both the aneurysmal sac and the cavity microscopically. Review of the slides in the other 2 cases, in which an aneurysm was not found, suggest that both the pulmonary and the bronchial arteries were injected with contrast medium.

*Origin in pulmonary artery* The pulmonary artery was identified on gross dissection as the source of the aneurysm in 7 of the 36 cases in which Rasmussen's aneurysms were found. In 2 additional cases the relatively large diameter of the vessel of origin (4 mm and 3 mm) in the mid-portion of the lung where the aneurysms were found point to involvement of the pulmonary rather than of the bronchial arteries. Arterial injection studies indicate that in one case the pulmonary artery was definitely the site of the aneurysm and in another case that it probably was. Thus, in 10 of the 36 cases in which an aneurysm was found, the pulmonary artery was definitely identified as the site of the aneurysm, and in another case the evidence pointed strongly to a similar source. The bronchial artery was not demonstrated as a source of fatal hemorrhage in any case in this series.

### *Histologic Studies*

Histologic studies of 34 aneurysms, 3 of which were examined in serial sections, revealed a picture which was fairly uniform and which varied only in details.

Cavity formation was always present and there was always some evidence of chronicity. Pericavicular fibrosis was always present, but the degree and extent varied considerably. In most cases the fibrosis involved all of the wall as represented in the microscopic sections and usually measured a millimeter or more in thickness. Deep in this zone and lining the cavity was a layer of caseous necrosis with or without an intervening zone of granulation tissue. In several cavities small patches of squamous epithelium were occasionally encountered.

In most of the cases in which the parent vessel could be followed, the course of this vessel was almost tangential to the wall of the cavity. As the vessel approached the wall of the cavity it passed through a zone of diseased pulmonary tissue and usually started to dilate slightly. Concomitantly, a variable degree of endothelial thickening usually occurred so that the lumen of the vessel was slightly constricted (figure 3). Similar obliterative endothelial changes were observed in the other large vessels in the vicinity of the cavity wall. In those other vessels which did not give rise to aneurysms and which actually encroached on the vomica, however, the obliteration of the lumen was complete. Serial sections revealed that the vessel wall proper dilated eccentrically, the dilatation taking place only on the side towards the lumen of the cavity. Finally a point of rupture of the media was encountered. At this point the walls of the media retracted quickly or were reflected back on themselves at an acute angle (figure 4). Through this defect the thickened endothelium protruded and formed the lining of the sac (figure 5). Fibroid changes, emphasized by Auerbach (5), were usually seen in the ruptured aneurysms and were frequently seen in the unruptured ones. This change usually started in the thickened endothelium at a point where the vessel wall was intact and it increased in thickness as it slowly spread over the lining of the vessel, usually forming a conspicuous part of the wall of the aneurysm near the neck of the sac (figure 6). Surrounding the endothelial layer, with or without the associated fibroid changes, was a relatively thick wall near the junction of the aneurysmal sac with the vessel. This wall usually contained a

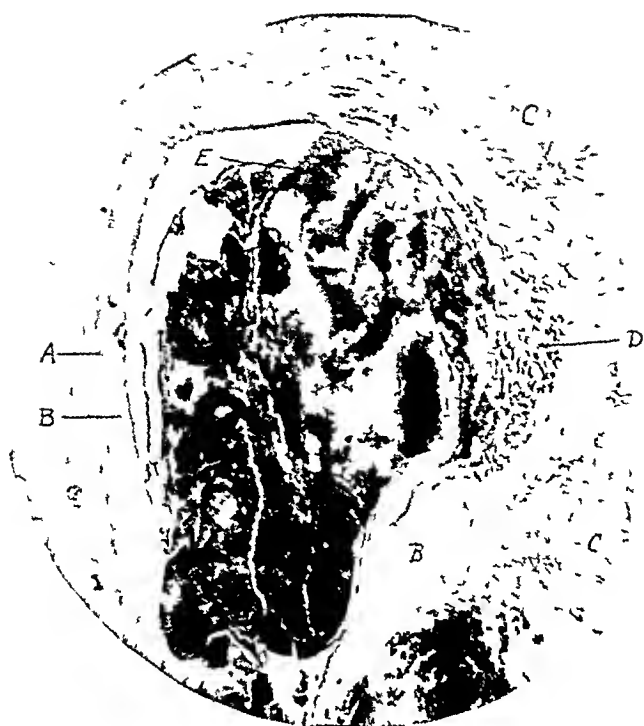


FIG 3 (Top) Microscopic section of aneurysm shown in figures 1 and 2 A, media of artery, B, thickened layer of endothelium, C, caseous necrosis lining cavity and covering aneurysm, D, fibrinoid degeneration, I, fibrin clot

FIG 4 (Bottom) Microscopic section showing reflection of ruptured media A, media of artery, B, lumen of aneurysm, C, fibrinoid degeneration, D, fibrin clot



FIG 5 (Top) Unruptured aneurysm A, cavity wall, B, media of artery, C, thickened endothelium, D, fibrin clot, E, fibrinoid degeneration, F, granulation tissue, G, caseous necrosis

FIG 6 (Bottom) Unruptured aneurysm A, lumen of cavity, B, vessel of origin, C, thickened endothelium with fibrinoid degeneration, D, lumen of aneurysm, E, fibrin clot, F, caseous necrosis

conspicuous amount of collagenous tissue. Occasionally a part of the wall of the aneurysm at this point was composed of granulation tissue in which were numerous, dilated, thin-walled blood vessels. In several instances this granulation tissue zone composed the bulk of the wall of the aneurysm, extending from the zone of fibrinoid degeneration outward. The combination of these two processes, fibrinoid degeneration and formation of granulation tissue, thus removed all trace of the preceding endothelial change. The most superficial layer of the aneurysm was usually a thin zone of caseous necrotic tissue.

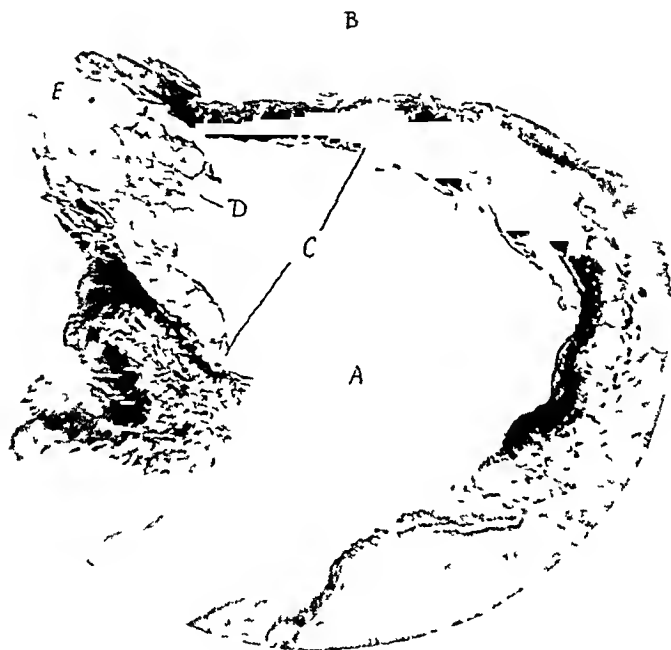


FIG 7 Ruptured aneurysm. Note the small amount of fibrin present in the aneurysm sac. A, lumen of aneurysm, B, lumen of cavity, C, walls of aneurysm, D, fibrin clot, E, point of rupture.

Within the sac, laminated layers of fibrin were usually seen. These were usually scanty near the neck of the sac and more numerous and denser in the upper portion. This mass of fibrin was always seen in the unruptured aneurysms and it was usually present in the ruptured ones. In several patients dying of massive terminal hemorrhage, however, this mass of fibrin was absent (figure 7).

#### DISCUSSION

It has been repeatedly emphasized in the past that the development of Rasmussen's aneurysms and the resultant massive hemorrhages tend to occur in the more chronic forms of cavity pulmonary tuberculosis (3, 4, 5, 11, and 15). Support for this concept is seen in the fact that these patients in general tended to have a longer duration of their disease than the average patient who died of tuberculosis, and the disease was predominantly fibrocaseous in admission.

roentgenograms Thirty-three of the 49 who died of hemorrhage had clinical symptoms referable to pulmonary tuberculosis for ten months or more before the fatal hemorrhage All of these 33 cases were diagnosed as having fibrocaceous pulmonary tuberculosis at autopsy Of the 16 patients who had clinical symptoms of pulmonary tuberculosis for nine months or less, and who subsequently died as a result of a massive pulmonary hemorrhage, all but 2 had fibroid or fibrocaceous disease histologically In these 2, with duration of symptoms of five and seven months, the disease was chiefly exudative with only small foci exhibiting early signs of organization. Further pathological evidence of chronicity was seen in the foci of squamous epithelium lining some cavities, the pericavernous atelectasis and cuboidal metaplasia of the alveolar linings, saccular or cylindrical bronchiectasis, and the focal or extensive obliterative pleural fibrosis

In addition to evidence of chronicity in the series of aneurysms, another noteworthy pathological feature is the fact that in all cases where the course of the vessel into the aneurysm could be traced, this course was tangential to the wall of the cavity The artery therefore approaches the cavity through a relatively thick zone of fibrotic scar tissue which may interfere with the circulation in the vasa vasorum derived from the bronchial arteries (16) which are the nutritional vessels for the pulmonary arteries In addition, intimal proliferation increases the thickness of the wall and adds to the problem of the supply of nutrition to the wall Thus, when a portion of the wall is finally involved focally by a tuberculous process, the defense mechanism is inadequate, the wall is weakened, and focal dilatation occurs, with the formation of an aneurysm In addition to the focal involvement of the wall of the vessel because of its tangential approach to the cavity, the loss of normal support in this same area aids in the formation of the aneurysm

The fibrous encapsulation of the vessel of origin, in addition to aiding in the formation of the aneurysm, may also play a part in permitting massive hemorrhage to occur A vessel encased in such rigid fibrotic tissue is less able to contract sufficiently to diminish effectively or to stop the bleeding

One factor exists, however, which may temporarily or permanently stop the bleeding This is the fibrin clot (3 and 5) which is formed in the sac as the aneurysm develops Such a fibrin clot is seen in every unruptured aneurysm and absent in many of the ruptured aneurysms The 23 cases in this series which had one or more fatal hemorrhages prior to the fatal one support Rasmussen's theory that this fibrin clot may occasionally plug the rent in the aneurysmal sac and thus stop the hemorrhage for a variable period If the fibrin clot is completely extruded, however, a valuable defense against fatal hemorrhage is lost Even if this valuable defense is lost, other factors may control the bleeding reduction of pressure and rate of flow in the pulmonary circuit, the tamponade effect of blood accumulating, and occasionally the clotting of the blood in the cavity and communicating bronchi

Such clot formation in the bronchi has been dramatically demonstrated by Wilson (17) in a case with massive pulmonary hemorrhage Spontaneous cessation of the hemorrhage was followed in three days by signs and roentgenographic evidence of massive atelectasis of the right lung. Four days later the patient



coughed up two large bronchial blood casts, after which the atelectasis cleared and the lungs returned to their previous status. After eight more months of bed rest, the patient's tuberculosis was considered arrested. Jackson and Diamond (10) have reported a similar occurrence in hemorrhage of nontuberculous origin.

Rasmussen noted the occurrence of occult hemorrhage as a cause of death. Likewise, in 3 cases in this series the patients who had had no previous hemorrhage were found dead in bed unexpectedly. On external examination there was no obvious explanation for death. At necropsy large quantities of blood were found in the lungs and bronchi. At least four different factors may have been instrumental in producing death in such a fashion: (a) suffocation from sudden aspiration of blood and obstruction of the bronchi, (b) debilitation of sufficient degree that the effective clearing of the bronchi by coughing could not take place, (c) reflex laryngeal spasm from foreign material (blood) in the bronchi and trachea, and (d) cerebral anoxemia. Sudden massive pulmonary hemorrhage may result in reduction in the pressure of the lesser circuit, just as shock develops from hemorrhage from the systemic circulation. This drop in pressure would lead to a reduced return of blood to the left side of the heart with resulting forward cardiac failure and inadequate blood flow to the brain. One or more of these factors may well play a part in the mechanism of death in any of the 36 cases in this series in which death occurred immediately after a massive pulmonary hemorrhage.

#### SUMMARY

1. A series of 56 cases is presented, in 49 of which death occurred as a result of massive pulmonary hemorrhage. These cases represent 7.2 per cent of 667 autopsies performed during a ten-year period. The source of this hemorrhage was identified as a Rasmussen's aneurysm in 29 cases and a similar source of hemorrhage is postulated from the remainder. In 7 other cases an unruptured Rasmussen's aneurysm was discovered as an incidental finding at autopsy.

2. Aneurysms and fatal pulmonary hemorrhage tend to occur more frequently in cases with a more chronic type of tuberculosis, both clinically and pathologically. Age, sex, race, and the presence of syphilis have no apparent significance in the development of these aneurysms.

3. A branch of the pulmonary artery could be identified as the site for the formation of the aneurysms in 11 cases. About one-half of the aneurysms which were located occurred on the medial wall of the cavity.

4. Perivascular fibrosis is discussed as a factor in the pathogenesis of Rasmussen's aneurysms and as a handicap to the control of bleeding from such an aneurysm.

5. Some of the factors contributing to death as a result of pulmonary hemorrhage are discussed.

#### SUMARIO

*Aneurismas de Rasmussen y Hemorragia Letal en la Tuberculosis Pulmonar*

1. En 49 de los 56 casos de la serie presentada, la muerte sobrevino a consecuencia de hemorragia pulmonar masiva. Esos casos representan 7.2 por ciento

de 667 autopsias ejecutadas durante un decenio La causa de la hemorragia fué identificada como aneurisma de Rasmussen en 29 casos y presúmese que fué semejante en los demás En otros 7 casos, se descubrió fortuitamente en la autopsia un aneurisma de Rasmussen intacto

2 Los aneurismas y la hemorragia pulmonares letales suelen ocurrir más frecuentemente en los casos con la forma más crónica, tanto clínica como patológicamente, de la tuberculosis La edad, sexo, raza y presencia de sífilis no guardan aparentemente relación con la formación de esos aneurismas

3 En 11 casos pudo identificarse una rama de la arteria pulmonar como asiento para la formación del aneurisma Aproximadamente la mitad de los aneurismas localizados quedaban en la porción media de la pared de la caverna

5 La fibrosis perivascular es discutida como factor en la patogenia de los aneurismas de Rasmussen y como obstáculo al tratar de cohibir la hemorragia procedente de unos de esos aneurismas

6 Repásanse algunos de los factores que contribuyen a la muerte debida a una neumorragia

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# TUBERCULOSIS OF THE TRACHEA AND MAJOR BRONCHI<sup>1,2,3</sup>

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## INTRODUCTION

In 1937 at a symposium upon inflammatory diseases of the bronchi, in which the writer (1) was one of the participants, great stress was laid upon the high frequency of clinically demonstrable tuberculosis of the trachea and major bronchi. This appeared to be at variance with our autopsy experience.

In an effort to evaluate the pathologic anatomy of the disease it was decided to study the trachea and major bronchi in 1,000 consecutive autopsies on tuberculous patients. Where gross lesions were present, sections were taken for microscopic study. In the absence of gross lesions, routine sections were taken from the posterior wall of the trachea and major bronchi.

## COMPOSITION OF SERIES

*Incidence* In 421 cases (42.1 per cent) there was evidence of tracheobronchial tuberculosis, 222 of these showed gross ulceration, 187 showed only microscopic evidence of tuberculosis, while in 12 it was secondary to a rupture of a regional lymph node into the tracheobronchial tree.

*Age* The age distribution (table 1) parallels very closely that in the general autopsy series. This is readily explained by the fact that the greatest number of cases in the general series died of chronic pulmonary tuberculosis, of which tracheobronchial tuberculosis in most instances is a complication.

*Sex* There were 266 (63.2 per cent) men in this group and 155 (36.8 per cent) women. This compares with 71.5 per cent men and 28.5 per cent women in the general autopsy series. Thus it would appear that tracheobronchial tuberculosis tends to develop a little more frequently in female than in male patients with tuberculosis.

*Color* White individuals were affected 234 times (55.7 per cent), Negroes 183 times (43.4 per cent), and Asiatics four times (0.9 per cent). The general autopsy series shows 61.3 per cent whites, 37.6 per cent Negroes, and 1.1 per cent Asiatics. The greater incidence in Negroes may be attributed to a difference of the pulmo-

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<sup>2</sup> Presented before the Medical Section, as part of the symposium on *Streptomycin and Extrapulmonary Tuberculosis*, at the 45th annual meeting of the National Tuberculosis Association, Detroit, Michigan, May 4, 1949.

<sup>3</sup> Sponsored by the Veterans Administration and published with approval of the Chief Medical Director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

<sup>4</sup> This material was gathered while the author was at Sea View Hospital, Staten Island, New York.

nary disease, which is frequently a more acute process among that race. Here there is a greater likelihood of spread to the intestine and tracheobronchial tree.

*Associated pulmonary tuberculosis* Chronic pulmonary tuberculosis was present in 405 instances in this series. In 4 cases the lungs showed an acute miliary tuberculosis without any evidence of cavities in the lungs. The miliary foci in the tracheobronchial tree and those in the lungs in these 4 cases were part of a generalized miliary tuberculosis from an extrapulmonary focus. In 12 cases there was no evidence of tuberculosis in the lungs before the rupture of a caseous lymph node into the tracheobronchial tree.

*Duration of chronic pulmonary tuberculosis* The duration of illness (table 2) was calculated on the length of time during which the patient's sputum was positive for acid-fast bacilli. In the 405 cases of chronic pulmonary tuberculosis, 159 (39.2 per cent) had a duration of from one to twelve months, 70 (17.3 per cent) from thirteen to eighteen months and 48 (11.9 per cent) from nineteen to

TABLE 1

## Age

Age in years	1 to 10	11 to 20	21 to 30	31 to 40	41 to 50	51 to 60	60 and over
Cases	4	51	111	117	65	47	16

TABLE 2

## Duration of Chronic Pulmonary Tuberculosis

Months	Up to 12	13 to 18	19 to 24	25 to 30	31 to 36	37 to 42	43+
Cases	159	70	48	22	22	3	81

twenty-four months. In 128 (31.6 per cent) cases the pulmonary disease was present for two years or more.

*Associated "tract tuberculosis"*<sup>1</sup> In 218 (51.8 per cent) cases in this series there was a concomitant involvement of the larynx, intestinal tract, and the tracheobronchial tree. In 127 (30.1 per cent) instances the tracheobronchial tree and the intestines were affected. In only 63 (14.9 per cent) of the cases in this series was the involvement limited to the trachea and major bronchi. In 13 (3.2 per cent) of the cases the "tract tuberculosis" was limited to the larynx and the tracheobronchial tree.

It is of interest that tracheobronchial tuberculosis is part of a tendency toward the development of "tract tuberculosis" in the great majority of cases (85 per cent). In the large majority of cases in this series the tuberculous process in the various tracts was a rapidly progressing one and was associated with an advancing chronic pulmonary tuberculosis.

## PATHOLOGIC FINDINGS

*Distribution* The type and distribution of lesions (table 3) reveals an interesting contrast when the gross and microscopic findings are compared. A survey of

<sup>1</sup> In the interests of simplicity, the term "tract tuberculosis" is used in this paper to designate involvement of the laryngeal and gastrointestinal tracts.

EXTENT OF TRACHEO BRONCHIAL INVOLVEMENT		TRACHEA AND BOTH MAJOR BRONCHI			TRACHEA AND RIGHT MAJOR BRONCHUS			TRACHEA AND LEFT MAJOR BRONCHUS			TRACHEA ONLY			RIGHT MAJOR BRONCHUS			LEFT MAJOR BRONCHUS			RIGHT AND LEFT MAJOR BRONCHUS		
		Ulcer	Foci	Total	Ulcer	Foci	Total	Ulcer	Foci	Total	Ulcer	Foci	Total	Ulcer	Foci	Total	Ulcer	Foci	Total	Ulcer	Foci	Total
Bilateral cavitation		15	7	52	40	13	53				20	9	29	42	33	75	3	29	32	5	32	37
Unilateral cavi- tation		20	0	20	16	4	20				8	4	12		5	17	10	13	23	8	15	23
Total		65	7	72	56	17	73	28	13	41	47	45	92	13	40	55	13	47	60	0	12	12

TABLE 3

*Distribution of Tracheobronchial Tuberculosis and Relation to Pulmonary Cavitation in 405 Cases of Chronic Pulmonary Tuberculosis*

the cases of gross ulceration shows only 26 cases in which the ulcers were found limited to either of the major bronchi. The trachea alone, or in combination with either or both major bronchi, contained ulcers in the remaining 196 cases. In those cases where the tracheal ulceration was present in association with bronchial ulceration, the ulcers in the trachea in some instances were either of the same anatomic age as those in the bronchus or even older. In these cases the ulcers were usually separated by intact mucous membrane. More often, however, the ulcers were more numerous and older in the bronchus than in the trachea and the tracheal ulceration was limited to the conchal region. Very often where the ulceration was present in the three segments there was extensive involvement of one major bronchus, while the tuberculous ulcers were limited to the inferior portion of the trachea and superior part of the opposite major bronchus. In the latter instances the progressive decrease in intensity of the process spoke for an extension from the greatly involved bronchus to the trachea and then on to the opposite major bronchus. This appeared to be the case in almost all of the 149 instances where the trachea and major bronchi were involved by the ulcerative process.

The presence of extensive ulceration in the trachea and major bronchi was invariably associated with an extensive and progressive pulmonary tuberculosis in which there was also an extensive tuberculous involvement of the intestinal tract and of the larynx.

*Relationship of site of cavities to tracheobronchial ulceration.* In each of the 222 cases with grossly evident ulcers, cavities were present in the lungs. It is noteworthy that in all cases where only one major bronchus was involved the cavities were always present on the same side. In those cases where bilateral cavitation was present, the greatest bronchial involvement was usually on the side of the older cavities.

The foci which were first discovered on microscopic examination were almost evenly distributed among the trachea and major bronchi. However, the presence of foci in two segments of the tracheobronchial tree was noted in a much less proportion than in the group with ulcerations.

*Location.* The classic ulcer may occur in any portion of the wall but shows a predilection for development on its posterior surface, then the lateral portion, and least frequently in the anterior aspects.

The ulcers may develop at any level in the tracheobronchial tree but show a definite tendency to develop at the concha. In many instances the tuberculous process is limited to the posterior wall of the conchal region. In occasional cases (three in this series) the tuberculous process was limited to the upper part of the trachea in its entire circumference. These were cases in which there was a direct progression from an extensive laryngeal tuberculosis.

*Gross appearance.* The size of the ulcers in this series varied from 1.0 mm. to 3.0 cm. The great majority of ulcers are from 1.0 to 5.0 mm. in size. Their long axes are parallel to the cartilaginous rings and they are lined by a yellow granular zone. Very often the intervening mucous membrane between the ulcers has a brown granular appearance. In this early stage the ulcers are usually present in the inferior aspect of the trachea or the superior aspect of a major bronchus on

the posterior wall. The presence of recent superficial ulcers of about the same anatomic age along the greater part of the trachea and major bronchi in some of the rapidly fatal cases speaks for a simultaneous infection of the tracheobronchial tree in these instances.

As the process continues, the ulcers increase in size and number. The ulcers appear in increasing number and first extend along the posterior wall. When the process begins in a major bronchus, the ulcers progress inferiorly and superiorly. In this latter extension it continues into the trachea and on to the superior por-

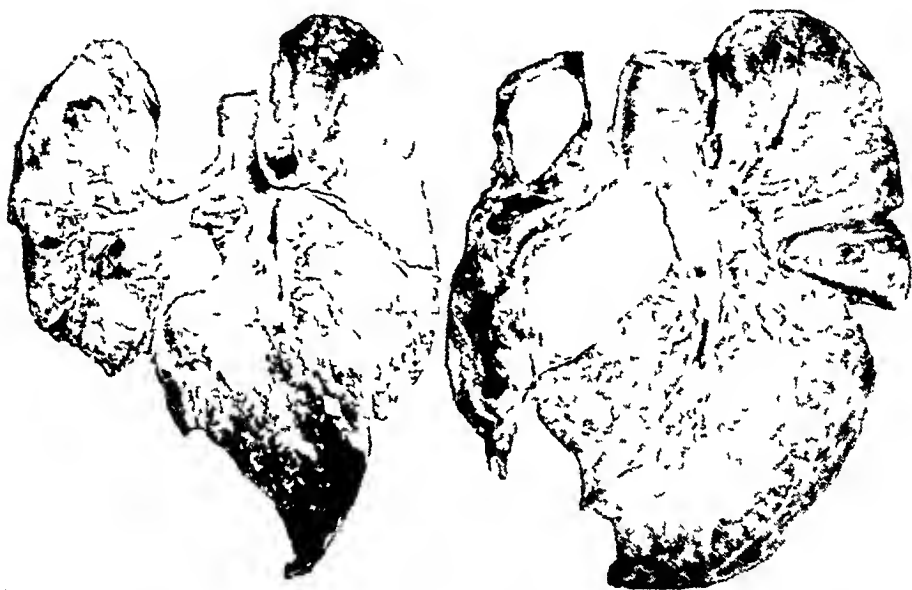


FIG 1 (Bronchial stenosis) (Left) Coronal section of the lungs of a 35-year-old woman who had chronic pulmonary tuberculosis for three years. There is a stenosis of the left major bronchus. The compressed lung is occupied almost exclusively by cavities and areas of caseous lobular pneumonia.

FIG 2 (Bronchial Stenosis) (Right) Coronal section of the lungs of a 51-year-old man who had chronic pulmonary tuberculosis for three and one-half years. The lumen of the stenotic left major bronchus measures 5 mm in diameter. The corresponding compressed lung contains a large cavity in the upper lobe, a slit-like cavity in the lower lobe.

tion of the opposite major bronchus. Progression of the tuberculous ulcers originating in the tracheal wall will be inferiorly toward a major bronchus and superiorly toward the larynx. With the enlargement and increase in number of the ulcers, fusion frequently occurs. In the far advanced cases only remnants of intact mucous membrane lie between the communicating ulcers.

In most instances the ulcers are superficial and cause no thickening of the wall of the tracheobronchial tree. Most of the cases of ulceration in this series are associated with a rapidly progressing chronic pulmonary tuberculosis and are of a relatively recent origin. An occasional case shows evidence of chronic ulceration, manifested by the presence of single or multiple, thick-walled ulcers usually

located on the posterior and lateral wall. The lumen of the tracheobronchial tree over these thickened ulcers becomes somewhat narrowed and somewhat distorted. In rare instances the cartilage may be partially exposed at the base of the ulcer.

Occasionally, the ulcerative process and the healing changes within the wall may be so extensive that they cause a marked narrowing of the lumen. In these cases the wall of the bronchus is thickened from 5.0 mm to 1.0 cm and the normal architecture is completely distorted by firm, grey, fibrous tissue. The

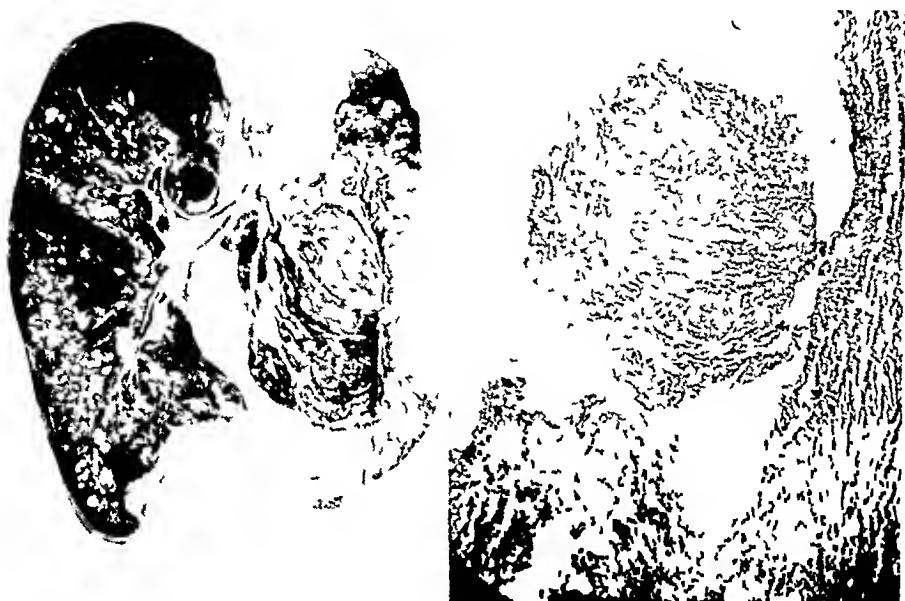


FIG 3a (Bronchial Stenosis) (Left) Coronal section of a 26 year-old woman who has chronic pulmonary tuberculosis for two years. The lumen of the stenotic right major bronchus measures one mm. in diameter. Caseous particles lie in the lumen of the bronchus. The circumference of the trachea is greatly narrowed as a result of healing of an extensive tuberculous process within it. The compressed right lung contains encapsulated caseous calcified foci chiefly in the lower lobe. There are no cavities in either lung.

FIG 3b (Right) Photomicrograph of the caseous mass and the wall of the bronchus (figure 3a). The caseous nidus lies free in the lumen. The inner wall of the involved bronchus is composed of granulation tissue and the outer aspect by hyalinized connective tissue.

lumen is narrowed from 2.0 to 1.0 mm in diameter and the stenosed bronchus is completely ulcerated. Large, irregular, caseous masses attached to the inner wall in one of the cases further narrowed the lumen of the bronchus (figure 3a).

*Microscopic appearance.* The evolution and the development of the tuberculous process in the trachea and bronchi are similar to these processes in the larynx and the gastrointestinal tract. The first changes are due to the presence of small oval and round foci within the wall. The size and number of these foci varies with the individual cases. The number varies from a single focus present in one of the three structures examined to many foci in all microscopic tissues examined. Most of the foci are located in the immediate subepithelial portion of the wall and in



the region of the mucous glands. In the more advanced process the foci are also present in the adventitial portions. Occasionally the foci within the wall are found only in the adventitia.

The foci in most instances are small and are typical epithelioid giant cell tubercles, with or without a central zone of caseation. The larger foci usually have a caseous center. In the great majority of instances the foci show no tendency towards progression but go on towards anatomic healing.

The development of the ulcer occurs in two ways from the enlargement of a subepithelial focus. First, the focus as it enlarges may cause a pressure atrophy of the overlying epithelium and when this is complete the focus may then rupture into the lumen and an ulcer is thus formed lined by an inner caseous wall. Second, a large caseous focus develops in the submucosa adjacent to the epithelium and in its progression envelops the mucosa in the caseous process. The caseous focus undergoes liquefaction and after pouring its contents into the lumen forms an ulcer lined by caseation.

Since the foci which develop into ulcers are small, the resultant ulcers are small also. A narrow zone of tuberculous vascular granulation tissue surrounds the inner zone of caseation. The caseous lining is replaced by a pyogenic membrane formed by the fibrin exuded from the capillaries of the vascular granulation tissue. The zone of granulation tissue is usually narrow and only occasional foci are present beyond it, thus accounting for the lack of thickening and distortion observed in the region of the wall of the ulcers.

In the later stages the foci beyond the zone of granulation tissue rupture into the lumen and the area of granulation tissue forming the wall of the ulcer widens. In a continuing process of progression and healing, much of the wall of the bronchus may be gradually destroyed. The mucous glands are destroyed and replaced by the tuberculous foci which develop in these zones. Similarly, the granulation tissue forming the wall of the ulcer widens, separates, and gradually replaces the mucous glands.

The cartilage is affected only in the very extensive process, in which instance it is involved by the encroaching granulation tissue. As the ulcer enlarges and borders of the granulation tissue zone widen, it erodes the perichondrium irregularly and later the cartilage. Occasionally, a rapidly progressing ulcerative process containing a wide inner wall of caseation extends to and surrounds the cartilage. When this undergoes liquefaction, a sequestrum of a cartilage plate lies at the base of the ulcer.

In the cases of bronchial stenosis, the tuberculous process is a chronic one in which there has been progression and repair for some time. The wall of the bronchus is greatly thickened by granulation tissue which separates and replaces most of the mucous glands and encircles and replaces to a variable degree the cartilaginous plates. This granulation tissue extends into the surrounding tissue for variable distances and contains many small and large foci, some of which contain a central zone of caseation. The stenotic bronchus contains an irregular ulcer which in some regions is lined by a pyogenic membrane, in others by caseation which in areas is irregular and protrudes into the lumen, and in still others by granulation tissue.

*Healing* Anatomic healing may occur in any stage of development of tuberculosis. It has been our experience that "tract tuberculosis" which is secondary to the original focus will in the vast majority of cases undergo healing if the source of tubercle bacilli is shut off. With closure of cavities in the lungs, healing of ulcers of the intestines, larynx, and tracheobronchial tree follows. Cavity closure follows closure of the bronchi at the bronchocavitary junction. In five instances in this series foci in the stage of anatomic healing were still present after the cavities had closed and the source of tubercle bacilli was cut off. The foci were still present from three to seven months after the closure of cavities and the disappearance of tubercle bacilli from the sputum.

In the majority of cases the tuberculous process in the trachea and bronchi is limited to small foci within the wall. When these undergo healing, they result in small areas of fibrosis and there is no distortion of the wall. Healing of ulcers occurs when the zone of vascular granulation tissue replaces the inner zone of caseation and the pyogenic membrane. With the increase of collagen fibrils, the cells and capillaries within the granulation tissue disappear and a zone of connective tissue replaces them. Regeneration of epithelium from all sides beyond the defect completely covers the ulcer. The regenerated epithelium now covers a zone of connective tissue in which an occasional capillary and epithelioid cell are present. With the final disappearance of the specific cells and capillaries the resultant connective tissue does not differ from that in noninvolved areas. At this stage it is impossible to identify this as the site of a healed ulcer. This will account for the discrepancy between bronchoscopy and autopsy findings when there is some interval between the last bronchoscopy and death. This occurs in the more chronic cases where healing of such ulcers occurs and not in the more rapidly progressing cases where the pathologist sees more extensive ulceration than the bronchoscopist.

Occasionally healing was noted in cases after much of the wall had been destroyed by deep ulceration and the presence of numerous foci. In these cases there is destruction of much of the cartilage, mucous glands, muscle, and elastic fibers. Healing results in the extensive fibrous replacement of the ulcer walls and the foci. Occasional remnants of normal structure lie within the scar tissue. Re-epithelialization of the healed ulcer is usually complete and the mucous membrane may have a smooth homogeneous surface, if the destruction was evenly distributed over one area, or a more corrugated appearance if there were irregular ulcers with intervening intact zones. In either event the circumference of the wall is greatly decreased in this region and the lumen may be narrowed to one-third of its original size (figure 3a).

#### DISCUSSION

There are three possible routes of infection of the trachea and major bronchi. These are (1) hematogenous, (2) extension from the neighboring structures, and (3) intracavitary infection.

*Hematogenous infection* The presence of miliary tubercles in the wall without ulceration in 187 cases raises the question of whether these may not have occurred by way of the blood stream. For this assumption to be valid, the foci in the

tracheobronchial tree would have to be part of a general hematogenous dissemination and similar foci would have to be present in other organs. A terminal miliary dissemination in the form of miliary tubercles in the viscera was observed in 72 of the 187 cases. The absence of hematogenous foci in other organs in the remaining 115 cases throws doubt on this as a usual route of infection. Another strong argument against the hematogenous route is the rarity with which miliary tubercles are found in the tracheobronchial tree in cases of acute generalized miliary tuberculosis. In this series there were only 4 cases in which the tubercles were part of an acute hematogenous dissemination. We agree with Cohn and Wessler (2), who observed one such case clinically, that the tubercles so formed play little or no role clinically.

*Extension from the neighboring structures.* In 12 cases a neighboring tracheobronchial lymph node extended through the wall and emptied its contents into the lumen of the tracheobronchial tree. The tuberculous process in these instances was limited to the region of the perforation and the opening was sealed by the adherence of the lymph node to the adventitia of the bronchus. The mass of caseation from the perforated lymph node may protrude into the lumen of the air passage and cause a decrease in its diameter.

The perforation into the air passages occurred in persons who had a progressive caseous tuberculosis of the lymph nodes of the mediastinum. In 4 instances the involvement of the lymph nodes was part of a primary complex and occurred in children. The other 8 cases occurred in adults and were part of a lymphohematogenous tuberculosis. There was an extensive caseous tuberculosis of the lymphatic system in the latter group.

Another possible mode of extension from the neighboring structures is a lymphatic drainage into the wall of the bronchus from the neighboring structures. This view has been advocated by Reichle and Frost (3) who felt that this is a more frequent mode of infection than implantation. They believe that the infection is carried from the lungs by way of lymphatics which are located in the adventitia. The lymphatic vessels lie near the mucous glands in the extracartilaginous region. Ornstein and Epstein (4) believed this to be the mode of infection in 8 clinical cases described by them. Subsequent observers have given little support to this mode of infection.

It is difficult to accept the views of Reichle and Frost (3) since tuberculosis of the air passages is rarely limited to the adventitia and then only in the form of an occasional tubercle limited to this zone. In the remaining cases the earliest changes are first observed in the submucosa just beneath the mucous membrane. With the advancement of the tuberculous process in the wall, the changes extend outward toward the adventitia. It is the writer's impression that tuberculosis in the tracheobronchial tree, like that in the larynx and gastrointestinal tract, begins in the mucosa and submucosa and progresses outward.

*Intracavitary infection.* With the exception of the occasional case of hematogenous dissemination and those with isolated foci in the adventitia, where the possibility of a lymphatic extension from a neighboring process exists, the infection of the air passages is the result of infected material passing over the mucous membrane.

The pouring out of numerous virulent tubercle bacilli must be considered an important factor since tracheobronchial tuberculosis occurs most frequently in the more rapidly progressing cases of chronic pulmonary tuberculosis. The more extensive ulceration is seen in the more acute cases of phthisis. This tendency for severe "tract tuberculosis" is not limited to the tracheobronchial tree, since these advanced cases are very often associated with extensive disease of the larynx and intestinal tract. Salkin, Cadden, and Edson (5) similarly found that the cases with tracheobronchitis showed a higher incidence of tuberculous lesions in the larynx and intestines and that it is a manifestation of a more malignant type of tuberculosis and represents a severer type.

The present observations, as well as most reports in the literature, show that tracheobronchial tuberculosis most often begins in the region of the coryna. The tubercle bacilli are carried through the lumen of the tracheobronchial tree and implanted in the wall. The corynal region corresponds to the ileocecal region of the intestinal tract as a site of predilection. Although sections of the branch bronchi in these cases will often show the presence of small foci in different parts of the walls, it is not the result of a continuous extension from the pulmonary cavities. To assume that the infection occurs by contiguity from the pulmonary infection, one would expect to see a continuous ulcerative process from the cavity along the bronchial wall. Continuous ulceration beginning at the bronchocavitory junction and extending to the major bronchus is a very infrequent occurrence in our experience. Meissner (6) examined the branch bronchi in surgically removed lungs for chronic pulmonary tuberculosis and found an irregular distribution of the tuberculous process in the various bronchi but no continuous ulceration. The present study shows that tuberculous ulcerations of the branch bronchi (except at the bronchocavitory junction where it is present in almost every case) is a very infrequent finding.

Reichle and Frost (3) believe that the strongest argument against the intracavicular theory is the absence of bronchial tuberculosis a few centimeters from a large cavity even though large quantities of infected sputum must have passed over this mucosa daily for weeks or months. Their argument also against comparing this mode of pathogenesis with intestinal tuberculosis is that the latter has an absorbing surface whereas the bronchus has not. It would, however, be difficult to explain a lymphatic extension to the larynx which has a similar incidence of tuberculous involvement and shows a similar mode of development and extension as that in the tracheobronchial tree.

*Incidence.* A review of the literature shows a marked variation in the reported incidence of tracheobronchial tuberculosis at autopsy. This varies from 3.1 per cent (7) to 72 per cent (8). In a previous report from our institution, Wilber (9) reported an incidence of 35.4 per cent. Most of the pathologic studies in the past two decades report an incidence which varies from 30 to 50 per cent.

It is believed that the reason for the great variation in the incidence lies in two important factors: (1) the type of case, and (2) the extent to which the tracheobronchial tree is studied. In the present series of 1,000 autopsies, all cases of tuberculosis were included (whether or not they had active chronic pulmonary tuberculosis). Thus, there were 92 cases without pulmonary tuberculosis and 30

other cases in which the chronic pulmonary tuberculosis had undergone anatomic healing, the patients having died of other causes (amyloidosis, cardiac failure, et cetera). As emphasized previously, the presence and the extent of tuberculosis in the tracheobronchial tree very frequently go hand in hand with rapidly progressing chronic pulmonary tuberculosis.

As would be anticipated, the extent of study of the tracheobronchial tree will greatly influence the incidence of lesions. The fact that 187 cases were first discovered on microscopic examination would clearly indicate that, if reliance were placed on gross examination alone, the incidence would only be 22.2 per cent. In the microscopic study, tuberculous foci limited to the trachea or either major bronchus were found in 138 cases, of which 34 showed the presence of only one or two foci. It is believed that, if more sections had been studied from different parts of the trachea and bronchi which on gross examination had appeared normal, more foci would have been found microscopically. This is in disagreement with the views of Bugher, Littig, and Culp (10) who state that a section chosen at random will accurately describe the entire trachea with the presence or absence of tubercles. While this may hold true in a few cases, in the majority of cases in the present series it could not be verified.

*Sex.* Much emphasis has been laid upon the preponderance of women over men with tracheobronchial tuberculosis. The incidence has been reported as high as 72 per cent (11), 75 per cent (12), and 85 per cent (13). It is interesting to note that this observation has been made chiefly in clinical studies, although a notable exception to this is the autopsy series of Sweeney and Behm (8). Our own findings show a slightly greater incidence of tracheobronchial tuberculosis in women than in the general autopsy series, but certainly not that reported in the clinical studies. This is interesting in that Myerson (14), in his clinical studies at the same institution in which this autopsy material was studied, states that women are affected three times more frequently than men. It is believed that this discrepancy may be accounted for in two ways: (1) Proportionately more women attend the bronchoscopic clinic than men, (2) many more men than women first enter the hospital in a far advanced stage of chronic pulmonary tuberculosis and are too ill to be seen by the bronchoscopist. The autopsy results as reported by Bugher, Littig, and Culp (10), Silverman (15), and Habershon (16) also show a marked preponderance of men over women.

*Associated laryngeal tuberculosis.* Laryngeal tuberculosis was present in 251 cases (59.6 per cent) in this series. In a previous study on laryngeal tuberculosis, the writer found an associated tracheobronchial tuberculosis in 57.5 per cent. In other autopsy reports (8 and 15), where similar comparisons were made, there is a similar frequent association.

While we agree with those authors (Bugher, Littig, and Culp (10) and Huang (17)), who claim that there is both pathologic and clinical evidence against the alleged development of a tuberculous tracheobronchitis secondary to laryngeal tuberculosis as suggested by Lederer (18), there are occasional cases (3 in this series) in which laryngeal tuberculosis may extend to the superior portion of the trachea. A similar observation was made by Samson (19) on bronchoscopic study and by Silverman (15) in autopsy cases.

In all other cases where both structures are involved, the tuberculous processes develop independently. Tracheobronchial tuberculosis develops in the corynal region most often, and laryngeal tuberculosis in the region of the vocal cords. As both processes advance, the former extends superiorly and the latter extends inferiorly, and in severe processes there may be an extensive ulcerative process which may extend from the tip of the epiglottis down into the major bronchi.

*Associated intestinal tuberculosis* It is rather interesting that in 81.9 per cent of the cases in this series there was an associated gastrointestinal tuberculosis. This is easily explained by the fact that in the entire autopsy series the incidence of intestinal tuberculosis is 70 per cent and in chronic pulmonary tuberculosis it is even greater. The incidence of laryngeal tuberculosis on the other hand is 37.5 per cent (20). It is, therefore, no surprise to find a much greater association with intestinal than laryngeal tuberculosis.

The writer is in agreement with Samson, Barnwell, Littig, and Bugher (21) who state that this tract involvement is associated with a common factor, chronic pulmonary tuberculosis.

*Location* The majority of the bronchoscopic and anatomic reports are in agreement with the present findings that most of the tuberculous ulcers are present in the posterior aspect of the tracheobronchial tree just above the coryna. Minkovsky (22), in a study of a large series of tracheal tuberculosis, found the most severe involvement in the majority of his cases to be in the lower part of the trachea. A notable exception is the study of Warren, Hammond, and Tuttle (23) who stated that the ulcers were not found especially along the posterior wall but rather about the orifices of the various bronchi.

It would appear from the present study that the frequency of tracheal ulceration and its relationship to bronchial ulcers is at variance with most reports, particularly the bronchoscopic observations. These authors (Acuna (24), Hawkins (25), Samson (19), and Wilson (11)) believe that ulceration in the trachea is less frequent than in the major bronchi. Some authors state that in most instances the tracheal lesion is an extension of the bronchial disease (Hawkins and Wilson) and that in almost every instance it is found on the same side and continuous with the bronchial ulceration (Wilson).

This discrepancy is more apparent than real. Since our cases in most instances represent a progressive process, it is no surprise to find extensive ulceration of the tracheobronchial tree. The site of predilection for the ulceration is the corynal region. Thus, in progression of a tuberculous process of either major bronchus, the opportunity for extension to the trachea is great.

The presence of 47 cases of tuberculous ulceration limited to the trachea, on the other hand, shows that isolated ulcerative tracheal tuberculosis is not a rare occurrence.

*Bronchial stenosis* Eloesser (26) gave this phase of bronchial tuberculosis much prominence when he stated that it was a stepchild of clinical medicine, that it was recognized too rarely, and that clinicians were not aware of how frequently it occurred. Subsequent clinical studies have emphasized the frequency of this complication in tracheobronchial tuberculosis.

Narrowing of the lumen of the tracheobronchial tree by a tuberculous process

may either be by the compression and extension of a tuberculous infection from without (extrinsic) or the development of a tuberculous process within the wall with subsequent narrowing of the lumen (intrinsic)

*Extrinsic process* In this series there were 12 cases in which the lumen of the bronchus was compressed by the neighboring lymph nodes. Later the caseous node ruptured into the lumen of the bronchus.

*Intrinsic process* Stenosis due to an intrinsic tuberculous process was encountered in 3 cases in this series. Prior to this study we encountered 3 similar cases. In all 6 cases there was a chronic ulcerative process with extensive destruction of the wall.

One of the 6 patients died of asphyxiation as a result of the aspiration of caseous particles to the opposite lung following bronchoscopy. Previous bronchoscopic treatments had given this patient relief when the narrowed lumen became obliterated by caseous particles and mucus. These findings appear to fit in with the views expressed by Andrews (27) that the stenosis is probably constant in this type of case at least (figure 3a), and the intermittency of symptoms is due to recurrent blocking of the narrowed lumen with caseous debris or thick mucus. Cases of asphyxiation due to a stenosis of the type just described have been reported by Schonwald (28), McConkey (29), and Crimm and Strayer (30).

It is difficult to explain the great discrepancy between the relatively great frequency of bronchial stenosis reported in clinical studies and the infrequency of such cases in the present autopsy series. Tuttle, O'Brien, Day, and Phillips (31) reported 92 such cases, of which 69 had an ulcerostenosis and 23 had a fibrous stenosis, and they state that the morbidity is great and fatality is high in ulcerostenosis. One possible explanation for the discrepancy may be the presence of an extensive edema in the wall of a bronchus containing tuberculous ulcers which greatly narrows the lumen. The edema disappears then with the patient's death. This view is given support by the clinical and pathologic studies of Salkin, Cad-den, and Edson (5) who state that one form of stenosis is an inflammatory swelling which is relative and is capable of being converted later to either a true stenosis or to an almost normal appearance.

In some of the cases of rupture of a caseous lymph node into the bronchus, the node first compressed and then eroded the bronchus. The eroded bronchus in these instances was lined by an irregular border of caseation extending in from the caseous lymph node (figure 4). It is possible that some of these cases might be interpreted bronchoscopically as intrinsic bronchial stenosis.

*Associated lung suppuration* Eloesser (26) states that more often than not cases of bronchial stenosis are complicated by suppurations and infections distal to the stenosis. Cohen and Higgins (32), in 19 patients with intrinsic bronchial obstruction complicating pulmonary tuberculosis, demonstrated bronchiectasis in 13, either by lipiodol installation or necropsy examination (4 cases). It should be emphasized that histological studies of the 4 necropsy cases showed tubercles in the walls of the bronchiectatic sacs and that there is no report of the isolation of pyogenic organisms. Chamberlain and Gordon (33), in a clinical study, emphasize that endobronchial tuberculosis is essentially a problem of mechanical ob-

struction with obstructive emphysema, bronchiectasis, and atelectasis is frequent complications. Other authors have also found that the sequelae of retained pyogenic organisms beyond the obstruction are fibrosis, bronchiectasis, and lung abscesses (34 and 35). It is significant that almost all of these reports are clinical studies.

The lung on the affected side in our cases was greatly diminished in size when compared with the opposite side. None showed any evidence of secondary infection and with it the sequelae which follow an obstruction of the lumen of the

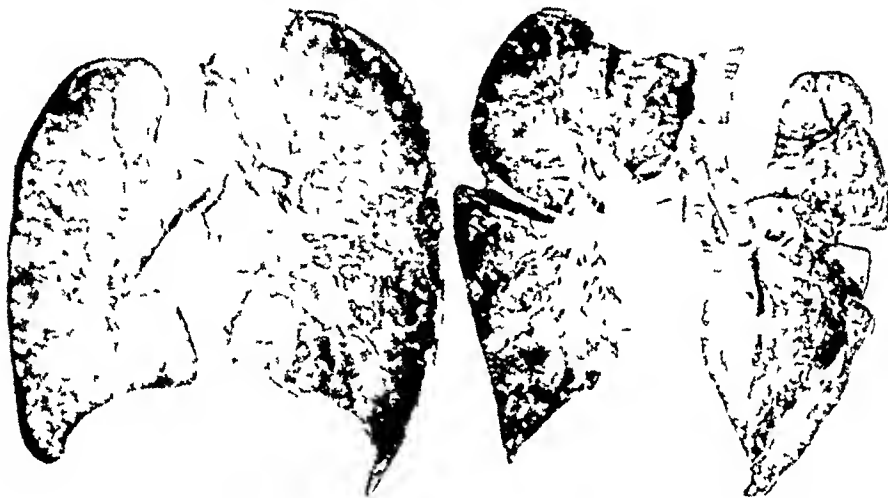


FIG. 4 (Rupture of lymph node into tracheobronchial tree) (Left) Coronal section of the lungs in a 16 year old boy who had a caseous tuberculous of the tracheobronchial lymph nodes as part of a lymphohemithogenous tuberculosis. His lung fields were clear and the sputum negative for tubercle bacilli before the rupture of the nodes into the tracheobronchial tree at the corner. The lumen of the left major bronchus is compressed by the enlarged caseous tracheobronchial lymph nodes.

FIG. 5 (Ulceration) (Right) Coronal section of the lungs of a 16 year old boy with chronic pulmonary tuberculosis of six months' duration. Pulmonary cavitation is limited to the right lung. Ulceration is present in the trachea and major bronchi and is most extensive in the right major bronchus.

bronchus so frequently observed in carcinoma of the major bronchus. It is interesting that the autopsy cases described by McConkey (29) and Cumm and Strayer (30) also showed changes similar to ours. Schonwald (28) in his case points out that the retained secretions contained tubercle bacilli but no other organisms.

In our experience, lung abscesses and/or suppurative inflammation of the tracheobronchial tree in the presence of chronic pulmonary tuberculosis is a rare occurrence, even under conditions where one would naturally expect them to occur. In almost every tuberculous cavity there is a great narrowing of the bronchus at the bronchocavitary junction, still it is rare to find pyogenic organisms in the vomica beyond the obstruction (36). Mixed infection tuberculous cavities are rare indeed and, even in cases of mixed infection empyema of the



pleural cavity in which bronchopleural fistulae are demonstrated, suppurative processes do not develop within the lung

Pyogenic abscesses were present in the lungs in 2 cases in this series. These were instances of extensive tracheobronchial tuberculosis in which portions of the cartilaginous rings are partially eroded and lay exposed. There was no stenotic lesion present in the tracheobronchial tree in these cases.

*Isolated tracheobronchial tuberculosis* In rare instances, at least in material observed at autopsy in a tuberculosis institution, the underlying tuberculous cavity may close and the tuberculous process within the tracheobronchial tree may progress. The writer has observed one such case which was not included in the present series. In this individual the cavity on the affected side had healed and the foci in this lung showed far advanced healing. The source of the tubercle bacilli in the sputum was the granulomatous caseous ulcer in the narrowed bronchus. Although we have observed this phenomenon in only one case, clinical observations appear to indicate that ulcerative tracheobronchial tuberculosis is not too infrequent a source of tubercle bacilli in the sputum. Alexander, Sommer, and Ehler (37) state that, with thoracoplasty in the presence of tuberculous tracheobronchitis, complete control of parenchymal lesions is not necessarily followed by anything like a corresponding improvement in the tracheobronchial lesions. Bainwell, Littig, and Culp (38) state that one of the most striking features of their 6 cases of ulcerative tracheobronchitis was the small extent of the pulmonary focus of tuberculosis when the patient first came under observation. They came to the conclusion, supported by bronchoscopic and pathologic studies, that tracheal and bronchial ulcers are a source of tubercle bacilli in the sputum. A similar view was expressed by Cohen and Wessler (2). Our case would lend some support to the claims that bronchial stenosis with caseous particles in the lumen may be responsible for tubercle bacilli in the sputum.

It is possible that ulcerative bronchitis may be a source of tubercle bacilli when the process is that of an ulcerogranuloma with large caseous particles in the lumen or that of a perforated liquefied caseous lymph node pouring tubercle bacilli into the lumen. In the usual ulcerative process after cavity closure in the lungs, the caseous inner lining, which is generally scanty, is soon replaced by granulation tissue.

#### SUMMARY

In a study of 1,000 consecutive autopsies on tuberculous patients, 421 were found to have tracheobronchial tuberculosis, an incidence of 42.1 per cent.

Tuberculosis of the trachea and major bronchi was in the vast majority of cases the result of an intracavitary infection from active and progressive chronic pulmonary tuberculosis. It was part of a tendency toward "tract tuberculosis" and occurred concomitantly with laryngeal and intestinal tuberculosis in 85 per cent of cases. A few cases (12) resulted from the rupture of a caseous lymph node into the tracheobronchial tree. Only 4 cases were associated with an acute hematogenous dissemination. That isolated foci in the adventitia were found in only an occasional case and that submucosal foci were far more frequent than adventitial foci suggest that extension to the trachea and bronchi through the lymphatics is a very rare route of infection.

Intrinsic bronchial stenosis was not found as frequently in this autopsy series as in clinical studies. In 6 cases of bronchial stenosis the lung on the affected side in each instance was contracted and in none was there any evidence of suppuration or bronchiectasis beyond the obstruction.

Pyogenic suppuration of the lung in chronic pulmonary tuberculosis is extremely rare and in the 2 cases in this series was associated with sloughing tracheo-bronchial cartilage and not with bronchial stenosis.

#### SUMARIO

##### *Tuberculosis de la Tráquea y los Bronquios Mayores*

En un estudio de 1,000 autopsias consecutivas en tuberculosos, 421 revelaron tuberculosis traqueobronquial, o sea una incidencia de 42.1 por ciento.

La tuberculosis de la tráquea y bronquios mayores fué, en la inmensa mayoría de los casos, resultado de una difusión intracanalicular de una tuberculosis pulmonar crónica, activa y evolutiva. Formó parte de una tendencia a "tuberculosis de las vías", coincidiendo con tuberculosis laríngea e intestinal en 85 por ciento de los casos. Algunos (12) casos provinieron de la rotura de un ganglio caseado en el árbol traqueobronquial. Sólo 4 casos se asociaron con diseminación hematógena aguda. El hecho de que sólo se descubrieran focos aislados en la adventicia en alguno que otro caso, y de que los focos submucosos fueran más frecuentes que los adventiciales, indica que la propagación a la tráquea y bronquios a través de los linfáticos constituye una vía muy rara de infección.

La estenosis bronquial intrínseca no fué observada tan a menudo en esta serie autopsica como en los estudios clínicos. En 6 casos de estenosis bronquial, el pulmón del lado afectado estuvo siempre contraído, sin haber nunca signos de supuración o bronquiectasia más allá de la obstrucción.

La supuración pulmonar es sumamente rara en la tuberculosis pulmonar crónica, y en los 2 casos de esta serie se asoció con esfacelo del cartílago traqueobronquial y no con estenosis bronquial.

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# PRESERVATION OF MYCOBACTERIA BY DESICCATION IN VACUO<sup>1</sup>

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## INTRODUCTION

Desiccation has long been known as a good bacteriostatic method for many saprophytic organisms. Desiccation *in vacuo* has recently been shown to be an effective, simple, and inexpensive means of preserving many species of fragile parasitic bacteria in a viable state over periods from a few months to 21 years (1). This report deals with the preservation of organisms of the genus *Mycobacterium* for over 17 years by desiccation *in vacuo*, using a method very similar to that referred to above.

In 1933 Harris and Lange (2) pointed out various disadvantages of maintaining actively vegetative bacterial cultures by monthly or bimonthly subculture; strains sometimes die out, contaminations occur, and the method is expensive, time-consuming, and troublesome. An additional disadvantage is the fact that variations in biological characters, including virulence, often occur. This has introduced considerable confusion into experimental studies of tuberculosis involving such strains as H37 and B1. The advantages of a simple method of preservation which maintains bacterial cells apparently unaltered, in a state of virtual suspended animation, without subculture, manipulation, or change of environment, for many years are obvious.

During studies on the preservation of acid-fast organisms in 1931, Harris and Lange prepared a half-pint milk bottle as a preserving vessel for vacuum desiccation of bacteria according to a method described by Brown (3) and stored within it a number of vials containing various strains of *Mycobacterium*. The jar was evacuated, closed with a desiccating agent in it, and reopened after eleven months.

The organisms were found viable, as reported, in 1932 (2).

The jar was again closed and stored in an obscure corner of a large refrigerator where it remained forgotten for about seventeen years. In the meantime, Dr Lange died and Dr Harris left Baltimore and one of us (MF) came into possession of the bottle which had remained in the refrigerator. In 1948 the bottle was transferred to Atlanta as part of a collection of desiccated cultures prepared and maintained for over twenty-one years. There it was opened and attempts were made to activate the bacteria which had remained forgotten for so long, dried *in vacuo*.

## FIRST ATTEMPT TO REACTIVATE THE CULTURES

The bottle was opened on August 5, 1948. The small manometer which had been placed inside the bottle, following the procedure of Brown, registered a

<sup>1</sup> From Laboratory Division, Communicable Disease Center, U S Public Health Service, Atlanta, Georgia.

vacuum of 43 mm, indicating virtually a perfect closure for seventeen years before the seal was broken. The following strains were selected for the first attempt at reactivation: Saranac H37 (human), B1 (bovine), B A I Pheasant (avian), and Butter R (saprophyte). The remaining strains were resealed *in vacuo* in another container and stored at refrigerator temperature. A heavy suspension of the desiccated material was prepared by adding about 0.2 ml of Tween-albumin medium (4) to the small vials and breaking up the hard kernels with a sterile wooden applicator stick. Smears prepared from the desiccated material revealed heavily beaded acid-fast rods.

The suspension was removed from the vials and added to approximately 5 ml of Dubos liquid (Tween-albumin) medium which served as the inoculum. Two tubes of Lowenstein-Jensen (5) medium, two tubes of Trudeau Committee (6) medium, and two tubes of Dubos Tween-albumin medium were each seeded with 0.3 to 0.4 ml of inoculum. The cultures were incubated at 37°C. Animal inoculations were also made with the suspended desiccated material as described later on.

On September 9, 1948, 4 human, 2 bovine, 2 avian, and 2 saprophytic strains were suspended in Tween-albumin medium as previously described and the suspension was used to inoculate two Lowenstein slants and two tubes of Tween-albumin medium for each strain, following the same procedure as described above.

On October 27, 1948, 3 more bovine strains, 4 avian strains, and 6 saprophytes were suspended in Dubos medium, then inoculated onto Lowenstein and Dubos media as before. No animals were inoculated with suspensions of the desiccated material in the last two series of cultures. Thus, a total of 5 human, 6 bovine, 7 avian, and 9 saprophytic strains were tested for viability by inoculation on to solid and liquid media.

#### RESULTS OBTAINED WITH DESICCATED MATERIAL

All of the human strains grew well on solid media and 4 grew in Tween-albumin medium. Three of the bovine strains grew well on Lowenstein medium while the other 3 grew with contaminants only in Dubos medium and were overgrown by contaminants on solid media. Pure cultures were obtained from the contaminated cultures and these were used for animal studies. These data are summarized in table 1.

#### VIRULENCE TESTS

*Desiccated material.* Dense suspensions in Tween-albumin medium were prepared on August 5 from the desiccated material of one vial each of the four major types: Saranac H37 (human), B1 (bovine), B A I Pheasant (avian), and Butter R (saprophyte). Each strain was inoculated subcutaneously into the inguinal region of guinea pigs, two animals being used for each strain. Bovine and avian strains were also inoculated intravenously into rabbits.

The desiccated bovine strain produced a few small lesions on the spleen of one of the guinea pigs, while the other guinea pig and the rabbit showed no



TABLE 2

*Autopsy Findings in Animals Inoculated with Subcultures of Desiccated Acid-fast Bacteria*

STRAIN	INOCULUM (mg)	ANIMAL	DEATH†	MICROSCOPY‡	LESIONS IN§					VIRULENCE§
					Lungs	Liver	Spleen	Nodes	Kidney	
<i>Human</i>										
Saranac H37	1	G P	K-42	+	—	—	—	+++	—	?
Lov 7	10 <sup>-1</sup>	G P	K-42	+	++	++	+++	+++	—	+
Lov 9	10 <sup>-1</sup>	G P	K-42	+	++	++	+++	+++	—	+
Lov 62	10 <sup>-1</sup>	G P	D-35	+	—	+	+++	+++	—	+
Lov 71	10 <sup>-1</sup>	G P	K-42	+	++	++	+++	+++	—	+
<i>Bovine</i>										
B 1*	1	G P	K-42	+	++	++	+++	+++	—	+
	1	Rabbit	K-57	+	+++	—	+	+	+	+
Zinsser B 1	10 <sup>-1</sup>	G P	K-42	+	—	—	+++	+++	—	+
	10 <sup>-1</sup>	Rabbit	K-60	+	+++	—	—	—	+	+
Opie B 1	10 <sup>-1</sup>	G P	K-42	+	—	++	++	+++	—	+
	10 <sup>-1</sup>	Rabbit	K-60	+	+	—	—	—	—	+
Hyg Lab 410	10 <sup>-1</sup>	G P	K-42	+	++	++	+++	+++	—	+
	10 <sup>-1</sup>	Rabbit	K-60	+	+++	—	—	—	—	+
<i>Avian</i>										
B A I Parrot	1	G P	K-42	—	—	—	—	—	—	—
		Chicken	D-60	—	—	—	—	—	—	—
B A I Swine	1	G P	K-42	—	—	—	—	—	—	—
		Chicken	K-60	—	+	—	en- larged	—	—	—
Van Es 3732	1	G P	K-42	+	(Atyp)	—	+	+	—	Unde- termined
		Chicken	D-19	—	—	—	—	—	—	Unde- termined
Van Es 4957	1	G P	K-42	+	—	—	—	+	—	—
		Chicken	K-50	+	+++	++++	++	—	—	+
Van Es Stock	1	G P	K-42	—	—	—	—	—	—	—
		Chicken	D-35	+	—	—	—	—	—	+
										(Yer- sin type)
B A I Pheasant	10 <sup>-1</sup>	G P	K-45	+	—	—	—	+	—	—
		Rabbit	K-84	+	—	—	—	—	—	+
										(Yer- sin type)
<i>Saprophyte</i>										
Butter R	5	G P	K-42	—	—	—	—	—	—	—
Timothy 6292	5	G P	K-42	—	—	—	—	—	—	—
Saranac	5	G P	K-42	—	—	—	—	—	—	—
Timothy										
"Lepra B"	5	G P	K-42	—	—	—	—	—	—	—
B Lepra	5	G P	K-42	—	—	—	—	—	—	—
A M										
B moelleri	5	G P	K-42	—	—	—	—	—	—	—
B smegmatis	5	G P	K-42	—	—	—	—	—	—	—
B E S	5	G P	K-42	—	—	—	—	—	—	—
Red Timothy	5	G P	K-42	—	—	—	—	—	—	—

\* Desiccated material direct

† Figures in this column are days from inoculation K = Killed, D = Died

‡ Acid-fast rods seen (+) or not seen (—)

§ Virulent (+) or avirulent (—)

|| Relative numbers of tubercles or extent of lesions are indicated by plus signs + to +++++

\*\* Superficial inguinal node only

medium, then suspended in sterile saline to give the following suspensions human  $10^{-1}$  mg per ml, bovine,  $10^{-1}$  mg per ml, and avian, 1 mg per ml. One ml of each suspension was inoculated subcutaneously into the inguinal region of a guinea pig. One rabbit was inoculated intravenously with 1.0 ml of each bovine suspension and one chicken was inoculated intravenously with 1.0 ml of each avian suspension.

All guinea pigs surviving forty-two days after inoculation were killed and autopsied while the rabbits and chickens were killed after sixty days. The lymph nodes, spleen, liver, and lungs of the guinea pigs and rabbits were examined for macroscopic lesions. Smears were prepared from the lesions, stained by the Ziehl-Neelsen technique and examined for acid-fast bacilli. The mesenteric lymph nodes, spleen, liver, and kidneys of the chickens were examined. Smears were prepared and examined for acid-fast bacilli. Virulence tests were not done on Princeton 32 (bovine), Park 643 (bovine), and Van Es H3701 (avian) because the cultures were lost through contamination. The results of the virulence tests are summarized in table 2.

As seen in the table, all of the strains on which tests were completed were found to be fully virulent except that Saranac H37 (human) appeared to be avirulent for guinea pigs, while Opie B 1 (bovine) was virulent for the guinea pig but exhibited low virulence in the rabbit. The strains B A I Parrot and B A I Swine (avian) were avirulent for chickens.

No exact data are available as to the original virulence of these strains. There is reason to believe that some laboratory stock cultures of the H37 and B1 strains used by investigators in 1931 were of low virulence (7). Fairly extensive lesions were produced by these strains in guinea pigs inoculated in 1932 (2). Rabbits were not inoculated at that time. It is impossible to state whether or not changes in virulence of the other organisms in this series occurred, because no exact information is available as to the level of their virulence when first desiccated.

#### SUMMARY

Twenty-seven strains of acid-fast bacilli were involved in this study. Of these, 18 were *M. tuberculosis* (5 human, 6 bovine, and 7 avian), and 9 were various saprophytes (such as *M. smegmatis*, *M. leprae*, "timothy" (*M. phlei*)). These bacteria were desiccated in a vacuum bottle in 1931, stored in a refrigerator, and remained undisturbed for seventeen years until 1948 when the bottle was opened and attempts were made to reactivate the cultures.

On introduction into appropriate media, all strains grew readily. Their morphology, staining properties, and virulence appeared unchanged. A few were lost because of overgrowth by contaminants, but sufficient growth of acid-fast bacilli occurred to demonstrate the viability of microorganisms. One human (Saranac H37), one bovine (Opie B 1), and two avian (B A I Parrot and B A I Swine) strains of *M. tuberculosis* were avirulent but all of the other strains of tubercle bacilli were fully virulent. No data were available as to the state of virulence of the cultures when originally desiccated, but it is thought that the human strain H37 may have been of low virulence to begin with.



## CONCLUSIONS

Desiccation *in vacuo* is a simple, inexpensive, readily available method of preserving acid-fast bacilli for long periods of time. The only special equipment needed is a good vacuum pump, a one-pint Mason jar, a dehydrating agent ( $\text{CaSO}_4$ ), and plasticine or other plastic material (1). With this method, standard laboratory strains, including freshly isolated strains and "vaccine strains", may be stored or shipped great distances without difficulties or concern over space, dehydration, or breaking up of culture media.

## SUMARIO

*Conservacion de las Micobacterias por la Desecacion al Vacio*

En este estudio figuraron 27 cepas de bacilos acidorresistentes: 18 del *M. tuberculosis* (5 humanas, 6 bovinas y 7 aviañas) y 9 de varios saprofitos (tales como, *M. smegmatis*, *M. leprae*, *M. phlei*). Esas bacterias fueron desecadas en un frasco al vacío en 1931 y colocadas en un refrigerador, en el que permanecieron sin ser tocadas durante diecisiete años, hasta 1948, fecha en que se abrió el frasco y se trató de reactivar los cultivos.

Al ser introducidas en medios apropiados, todas las cepas proliferaron sin dificultad, sin cambio aparente en morfología, propiedades de tinción y virulencia. Algunas se perdieron por excesivo desarrollo de gérmenes contaminantes, pero hubo suficientes colonias de bacilos acidorresistentes para demostrar la viabilidad de los mismos. De las cepas de *M. tuberculosis*, una humana (Saranac H37), una bovina (Opie B1) y 2 aviañas (B A I Papagayo y B A I Cerdo), resultaron avirulentas, pero todas las demás eran plenamente virulentas. No hay datos relativos al estado de virulencia de los cultivos al ser desecados primitivamente, pero parece que la cepa humana H37 puede haber poseído poca virulencia para dicha fecha.

## CONCLUSIONES

La desecación al vacío ofrece un método sencillo, económico y de fácil empleo para la conservación de bacilos ácidosresistentes durante períodos de tiempo prolongados. La única instalación especial necesaria consiste en una bomba neumática, un jarro de Mason de  $\frac{1}{2}$  litro, un deshidratador ( $\text{CaSO}_4$ ) y plastilina u otra sustancia plástica. Con este método, sin dificultad y sin preocuparse con respecto a espacio, deshidratación o desintegración de los medios de cultivo, pueden conservarse o remitirse a grandes distancias cepas corrientes de laboratorio, incluso las recién aisladas y las destinadas a la producción de vacunas.

*Acknowledgment*

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# TOXICITY OF SPUTUM DIGESTANTS TO TUBERCLE BACILLI IN WATER AND SPUTUM<sup>1</sup>

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## INTRODUCTION

Isolation of *M. tuberculosis* from contaminated pathological material can best be accomplished if proper methods of digestion and decontamination are used. Cultivation of *M. tuberculosis* on artificial media is slow and difficult, and requires special methods to prevent the multiplication of contaminating organisms commonly found in specimens from which tubercle bacilli must be isolated. It is essential that the methods employed to reduce contamination do not retard growth of tubercle bacilli. Despite the many improvements which have been suggested in cultural techniques, it is not always possible to initiate growth in cultures from microscopically positive specimens.

Preparation of specimens for smear, culture, or animal inoculation by digestion and concentration necessitates exposure of the material to various more or less toxic substances. The purpose of such treatment is to dissolve tenacious mucus and cellular debris and to kill secondary organisms. Theoretically an ideal digestant should be toxic to all organisms except the tubercle bacilli. This study was undertaken to help evaluate the relative toxicities of the most commonly used digestive agents.

The work is divided into two parts: (1) preliminary laboratory tests on aqueous suspensions of tubercle bacilli, (2) tests on homogenized sputum under practical diagnostic conditions.

## METHODS

### *Aqueous Suspensions*

A 3-weeks-old culture of H37Rv was harvested, weighed, and ground ten minutes in a sterile mortar with enough sterile distilled water to prepare a suspension containing 1 mg. of the bacilli per ml. Dilutions were prepared from this suspension containing  $10^{-2}$  and  $10^{-4}$  mg. of bacilli per ml. Each dilution was divided into 1 ml. amounts and mixed with equal volumes of the digestant: 4 per cent sodium hydroxide, 3 per cent hydrochloric acid, 5 per cent sulfuric acid, 2.5 per cent ammonium carbonate, and 10 per cent trisodium phosphate (anhydrous).

Exposure of the tubercle bacilli to the various digestants was brought about by combining the digestant in question, in the concentrations routinely employed with an equal volume of the bacilli in water, incubating for the desired interval at 37°C., mixing with a predetermined quantity of neutralizing agent (all such mixtures were adjusted to 10 ml. volume) and then seeding in amounts of 0.1

<sup>1</sup>From the Tuberculosis Evaluation Laboratory, Communicable Disease Center, Public Health Service, Atlanta, Georgia.

ml on each of 10 tubes of Jensen's modification of Lowenstein's medium. The total weight of bacilli thus transferred was  $10^{-5}$  or  $10^{-6}$  mg per tube of medium, according to the dilution used. This same procedure was repeated in testing each different period of exposure, each digestant, and each dilution of bacilli. In general the exposures were 10 minutes, 24 hours, 48 hours, and 72 hours.

Inoculations were made from the mixtures onto Jensen's modification of Lowenstein's medium (1) after exposing the bacilli for measured periods of time to the digestants. Controls were prepared by adjusting the reaction of the digestants to pH 7.0 before combining with the proper weight of culture. In a

TABLE I

*Total Colony Counts on 10 Tubes of Medium Inoculated with Aqueous Suspensions of Tubercle Bacilli Exposed to Various Digestants*

EXPOSURE TIME	5 PER CENT Na <sub>2</sub> PO <sub>4</sub>		2 PER CENT NaOH		1.25 PER CENT AM CARB		2.5 PER CENT H <sub>2</sub> SO <sub>4</sub>		25 PER CENT ANTIFERM		1.5 PER CENT HCl	
	Count	Per cent Surv.	Count	Per cent Surv.	Count	Per cent Surv.	Count	Per cent Surv.	Count	Per cent Surv.	Count	Per cent Surv.
10 <sup>-5</sup> mg Bacilli Per Tube												
Control*	582	100.0	506	100.0	163	100	478	100.0	157	100.0	100	100
40 Minutes	307	52.0	235	46.0	98	60	200	41.8	11	7.2	6	6
24 Hours	286	49.2	40	8.0	0	0	0	0	0	0	0	0
48 Hours	275	47.3	27	5.4	0	0	0	0	0	0	0	0
72 Hours	262	44.9	15	3.0	0	0	0	0	0	0	0	0
10 <sup>-6</sup> mg Bacilli per Tube												
Control*	173	100.0	68	100.0	48	100	93	100	79	100	83	100
40 Minutes	96	56.0	60	88.0	40	87	27	29	0	0	0	0
24 Hours	94	53.6	6	8.8	0	0	0	0	0	0	0	0
48 Hours	91	53.0	5	7.3	0	0	0	0	0	0	0	0
72 Hours	71	42.4	0	0	0	0	0	0	0	0	0	0

\* Medium inoculated immediately after mixing bacillary suspension and neutralized digestant (pH 7).

measure these served as controls because they gave an approximation of the number of bacilli present without the prolonged action of the digestants.

A carry-over of the neutralized salts of the digestants and neutralizing agent in the inoculum to the culture was recognized but, since the same salts were also inoculated onto the control tubes, this factor was not considered important.

The cultures were examined after two weeks of incubation and once weekly thereafter until five weeks of age. The total number of colonies present at five weeks on each set of 10 tubes was counted and recorded for comparisons. Repeated experiments, inoculating  $10^{-5}$  and  $10^{-6}$  mg of bacilli per tube of medium as described, gave essentially the same results each time. For the sake of brevity the results of only one experiment are given (table 1).

## RESULTS

### *Aqueous Suspensions*

From the results in table 1, it is evident that all of the digestants markedly reduced the number of viable bacilli within the shortest period likely to produce adequate decontamination. This table indicates that trisodium phosphate and sodium hydroxide are less toxic than the other agents tested. It is difficult to interpret the significance of the differences obtained with ammonium carbonate, sulfuric acid, antiformin, and hydrochloric acid. It is recognized that colony counts are somewhat variable but repeated tests gave similar results. The concentrations given are those actually in contact with the tubercle bacilli. It may be noted that the action of trisodium phosphate differs from that of the other reagents. Though approximately 50 per cent of the tubercle bacillus population was killed during 40 minutes, few microorganisms were destroyed during the remainder of the 72-hour period.

### *Sputum Suspensions*

Because of the possible protective effect of sputum (2) on tubercle bacilli, experiments in the absence of this material might portray an inaccurate picture of the relative toxicities of various digestants under practical conditions.

With this in mind 10 microscopically "positive" specimens of sputum were pooled and homogenized by shaking two hours in a paint-conditioning machine (3). This resulted in a completely uniform, slightly viscous fluid. In this experiment the following digestants were used: sodium hydroxide, trisodium phosphate, oxalic acid, sulfuric acid, ammonium carbonate, and hydrochloric acid. Each digestant was then mixed in 1 ml. amounts with equal volumes of the homogenized sputum and allowed to incubate for the desired time at 37°C. After the specified intervals the pH of the mixtures was adjusted to 7 with the necessary amount of acid or base in sufficient diluent to make a final volume of 10 ml.,<sup>2</sup> and inoculated onto 10 tubes of medium in 0.1 ml. amounts without further preparation.

The exposure periods during which the "positive" sputum was in contact with each of the digestants before neutralization were 20 and 40 minutes and 2, 24, 48, and 72 hours.

In order to compare the inherent toxicities of the reagents (apart from the pH produced), aliquots of the decontaminated and neutralized sputum were also incubated in a final volume of 10 ml. of the salt formed by neutralization of each digestant. These results did not differ from those obtained when sodium hy-

<sup>2</sup>The homogenized sputum was tested for combining power with different digestants, sodium hydroxide, sulfuric acid, hydrochloric acid, oxalic acid, trisodium phosphate, and ammonium carbonate. Three 1 ml. samples of each digestant were mixed with 1 ml. samples of the homogenized sputum and the reaction adjusted to pH 7.0 using bromthymol blue as an indicator, sodium hydroxide was used to neutralize the acids and sulfuric acid to neutralize the bases. To avoid the use of strong reagents on metaproteins, the neutralizing solutions were brought to a volume of 8 ml.

dioxide was neutralized with sulfuric acid. The loss of viability was very slow by comparison with that in the active reagents.

The toxicities of the digestants tested in the presence of sputum are shown in table 2. The toxicities of such digestants as were tested both in sputum and aqueous suspensions are seen to be comparable. Unfortunately antiform and oxalic acid were not tested under both conditions.

TABLE 2

*Total Colony Counts on 10 Tubes of Medium Inoculated with Homogenized Sputum Containing Tubercle Bacilli and Exposed to Various Digestants*

EXPOSURE TIME	NaOH 2 PER CENT		TRISODIUM PHOSPHATE 5 PER CENT	OXALIC ACID 2.5 PER CENT	H <sub>2</sub> SO <sub>4</sub> 2.5 PER CENT	AMMONIUM CARBONATE 1.25 PER CENT	HCl 1.5 PER CENT
	Full time exposure	Base* only 40 minutes					
20 Minutes	Inn con- tam	Inn con- tam	Inn con- tam	Contam	Inn con- tam	Contam	400
40 Minutes	Inn	Inn	Inn	Inn	Inn	Inn	140
2 Hours	Inn	Inn	Inn	Inn	1,000	1,000	0
24 Hours	580	1,000	1,000	0	0	0	0
48 Hours	0	700	270	0	0	0	0
72 Hours	0	400	60	0	0	0	0

Inn = Innumerable acid-fast colonies

Contam = contaminated

\* At 40 minutes the remainder of this series of NaOH tubes was neutralized.

Subsequent decline in viability serves to indicate the rate of death in neutralized sputum during the completion of the experiment.

#### DISCUSSION

Tison (4) claims that tubercle bacilli retain viability and infectivity up to 3 months in sputum held at 7° to 22°C, whereas in most sputum infectivity is lost after 4 days at 37°C.

Corper and Stoner (5) point out that trisodium phosphate in a concentration of 10 per cent (23 per cent Na<sub>3</sub>PO<sub>4</sub> · 12H<sub>2</sub>O) can remain in contact with small numbers of tubercle bacilli for as long as seven days at room temperature without destroying all of them.

Results of the experiments described in this paper tend to corroborate the findings of the latter two authors. Nevertheless, even in the case of the least toxic of the digestants, a marked diminution in the number of bacilli was found after short exposures. While our experiments were never continued for as long as 7 days, it is recognized as possible that some bacilli might survive that long if their original number is large enough and the temperature of the room is low enough.

In some laboratories sulfuric acid has been considered less toxic to tubercle bacilli than either hydrochloric acid or sodium hydroxide. For this reason "thin" specimens not requiring a potent digestant are generally treated with sulfuric acid in preference to sodium hydroxide. This conception probably stems from

the work of Corper and Uyei (6) who found that, of the large number of reagents investigated for isolating tubercle bacilli from contaminated tuberculous material, sulfuric acid was most serviceable "It possessed a wider range between its being innocuous for tubercle bacilli and its being capable of destroying undesirable contaminants than any of the others tested HCl and NaOH also proved satisfactory for this purpose, the former slightly more so than the latter, while urea, sodium carbonate, ammonium hydroxide and ammonium carbonate proved entirely unsatisfactory"

An explanation of these findings with the acids may rest in part on the likelihood of more efficient collection of the tubercle bacilli due to their occlusion in the bulkier sediments which result from acid treatment Low toxicity of digestant and facilitation of collection need not go hand in hand

According to the results of tests by the Tuberculosis Evaluation Laboratory, ammonium carbonate was also found less satisfactory than the other reagents However, repeated tests failed to show any advantage of sulfuric acid or hydrochloric acid over sodium hydroxide at any concentration studied Two per cent, 3 per cent, and 4 per cent sodium hydroxide were compared with 2.5 per cent, 5 per cent, and 6 per cent sulfuric acid and 1.5 per cent and 3 per cent hydrochloric acid Contrary to the experience of Corper and Uyei, it was found that sodium hydroxide was relatively less toxic to the tubercle bacillus than sulfuric acid and hydrochloric acid at the concentrations mentioned and relatively more toxic than trisodium phosphate, 10 per cent

#### CONCLUSION

Experiments were undertaken to compare the toxicities of various commonly used digestants Trisodium phosphate and sodium hydroxide appeared to be less toxic to tubercle bacilli than the other agents tested

#### CONCLUSIONES

#### *Toxicidad de los Digestantes del Espeto para los Bacilos Tuberculosos en Agua y en Espeto*

En las condiciones de los experimentos aquí descritos, los digestantes del espeto investigados ocuparon, en el orden de su toxicidad creciente, los siguientes puestos fosfato trisódico, hidróxido de sodio, ácido oxálico, ácido sulfúrico y ácido clorhídrico

#### *Acknowledgment*

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# THE COMBINED USE OF TRACHEAL LAVAGE AND CULTURE AS A DIAGNOSTIC PROCEDURE IN PULMONARY TUBERCULOSIS<sup>1</sup> \*

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## INTRODUCTION

The clinical evaluation of the minimal pulmonary infiltration is often difficult because of lack of bacteriological confirmation. This has always been true, but with the wide use of roentgenographic surveys the problem of determining whether or not a minimal lesion is active is being encountered with increasing frequency.

The chest physician often faces the following dilemma. Should he actively treat a patient who, in his judgment, has an active lesion but from whom no tubercle bacilli can be recovered? To do so means embarking that person upon a long course of treatment with the interruption of normal living, no small expense, psychic trauma, et cetera, and yet not to treat him actively calls for prolonged observation of one who does not consider himself to be ill, and incurs the risk of losing contact with the patient. It also means that the physician must accept the hazard of possible extension of the patient's disease and infection to his near associates.

Hilleboe advises observation of these patients. If an ideal follow-up and case-holding program are available, this is good epidemiology but does not always serve the best interest of the individual. Hilleboe is rightly concerned in avoiding the treatment of inactive lesions but, unless some accurate method of evaluating activity is available, there also exists the serious possibility that the treatment of active lesions may be delayed. This may be disastrous to the individual, and the individual after all is one of the physician's responsibilities. Consequently, the one upon whom the responsibility of decision rests is relieved if he has factual data regarding the activity of the lesion under consideration.

It would seem that the answer to this dilemma would lie in the availability of a sensitive, accurate, rapid, and simple method for the recovery of tubercle bacilli from the lesion in question. A very considerable advance has been made in this direction by the combined use of tracheal lavage and sensitive culture methods. The writers have been surprised by the high percentage of recovery of tubercle bacilli from such lesions by the combined use of these procedures.

For the purpose of this discussion it is assumed that all the usual methods of direct examination have been employed without success before the more elaborate and sensitive methods are undertaken.

<sup>1</sup> Presented at the annual meeting of the California Trudeau Society in San Francisco, California, on April 4, 1949.

<sup>2</sup> Much of the data used in this paper is from a study supported in part by the Alameda County Tuberculosis and Health Association.

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## ADVANTAGES OF TRACHEAL LAVAGE

Tracheal lavage as compared to gastric lavage has the following advantages

- (1) The material is obtained nearer the source of its origin and has not been diluted or dissipated
- (2) The organisms have not had their virility impaired by coming in contact with gastric acids and enzymes (important in culture or animal study)
- (3) It is not necessary to do the tracheal lavage upon a fasting stomach. It can be done any time of the day and is easily carried out as an office procedure
- (4) It is well tolerated by the patient, many patients state that "it is not nearly so bad as a gastric"

Culture, when carried out by a technician trained in its use and under the exacting conditions required, has the following advantages over animal inoculation

- (1) It is more rapid. When using Dubos media, positive cultures are obtained not infrequently within the period of ten days, but in an average from fourteen to twenty-one days
- (2) It is less expensive
- (3) It is at least as sensitive as animal inoculation
- (4) In spite of belief to the contrary, there is evidence that guinea pigs have some natural resistance to infection with the tubercle bacillus (1)

These combined advantages add up to a major advance in our ability to recover tubercle bacilli from the patient who sheds only a few organisms

## TECHNIQUE OF TRACHEAL LAVAGE

The technique of tracheal lavage is not difficult. Fasting is not required. If the patient has an active gag reflex, the pharynx may be sprayed with a 2 per cent pontocaine solution. For the very rare patient who may be sensitive to pontocaine, it is well to have an injectable barbiturate at hand. With the patient in a sitting position the tongue is drawn forward, the larynx is visualized with a mirror, and the laryngeal cannula tip is introduced between the vocal cords thus ensuring the introduction of the lavage liquid into the trachea itself. Then 5 cc. of sterile distilled water are quickly introduced through the cannula. The use of sterile distilled water is preferred to saline solution, since it has been reported that saline slows the growth of cultures of tubercle bacilli (2). The material coughed up is collected in a sterile container and concentrated for culture or guinea pig inoculation. Several tracheal instillations may be carried out at one sitting. The equipment required for tracheal lavage is simple and consists of the following:

- (1) No. 4 laryngeal mirror
- (2) A metal laryngeal cannula
- (3) A 5 cc. syringe
- (4) A head mirror

Because of the explosive character of the cough which sometimes occurs, it is well to wear a face mask or shield.

## COMPARISON OF MEDIA

Extensive experiments have been carried on in attempts to compare various media. Such studies are never without bias of some sort, since even the most scrupulous attempts to conduct a fair trial are usually shaded in favor of the medium with which the technician is most familiar. The technical details of the media used in the present study are being published elsewhere. Suffice it to say that in the writers' experience the media used line up as follows with regard to both sensitivity and speed of growth:

- (1) Dubos (oleic acid, solid medium with penicillin (3))
- (2) Herrold's medium (as described in the proceedings of the Staff Meetings of the Mayo Clinic (4, 5))
- (3) Official medium of the American Trudeau Society as modified at the latest session of the Research Committee (6)
- (4) Petragnani's medium
- (5) Petrick's medium (This medium was used in the laboratory for years and it is fairly sensitive, but requires considerable time for growth)

The above mentioned modified Dubos medium lends itself very well to the determination of sensitivity tests and overcomes the objections made by Williston and Youmans (7) and others, since it does not contain Tween or serum.

Dubos media in a solid form has been used to facilitate the study of the morphology of the colonies, which varies considerably. The morphology of the colonies gives an excellent index to virulence.

## TRACHEAL LAVAGE AS COMPARED TO GASTRIC LAVAGE

Tracheal lavage was performed on 199 patients with negative bacteriologic findings by direct methods of examination at Arroyo del Valle Sanatorium, Highland Hospital, Fairmont Hospital (all of Alameda County), and elsewhere. Tubercle bacilli were cultured (on Dubos medium) from the lavage specimens of 111 of these 199 patients. Gastric lavage had been performed in 86 of these 111 patients. In only 24 instances was the specimen of gastric washings positive for tubercle bacilli when cultured by various techniques.

In no instance were tubercle bacilli cultured from gastric lavage material obtained from a patient whose tracheal lavage specimens were negative for tubercle bacilli.

## GUINEA PIG INOCULATION AS COMPARED TO CULTURE (DUBOS)

Forty divided specimens were inoculated into guinea pigs and upon culture media. Twenty-seven of these were positive for *M. tuberculosis* upon Dubos culture, and 23 of the 27 were positive as reflected by the presence of gross lesions in the guinea pigs at autopsy. The remaining 4 animals which had been inoculated had positive tuberculin tests to 5 mg. of Old Tuberculin.

Since the start of this study two years ago at Arroyo del Valle and at Livermore Veterans Administration Hospital, there has been no instance of a "positive" guinea pig and a "negative" Dubos culture when examinations were done upon divided specimens.

GUINEA PIG INOCULATION AS COMPARED TO DUBOS MEDIUM AND AMERICAN  
TRUDEAU SOCIETY MEDIUM INOCULATION

Specimens obtained from 580 consecutive cases of tuberculosis were studied at Arroyo del Valle and Livermore Veterans Administration Hospital. Tubercle bacilli were cultured from the specimens from 269 patients. The specimens from 45 patients, however, yielded tubercle bacilli when cultured on Dubos medium but not upon guinea pig inoculation. The animals were tested with 5 mg. of Old Tuberculin and were examined for the presence of gross lesions at autopsy. Thirty-one of these 45 specimens also yielded tubercle bacilli when cultured on the American Trudeau Society medium.

All of the above 45 cases, which were positive to culture but negative to guinea pig inoculation, were checked by subinoculation into guinea pigs and all of the animals so inoculated developed positive tuberculin tests and had gross lesions at autopsy.

This should not be interpreted as a recommendation to abandon guinea pigs for diagnostic purposes. In hospitals which do not specialize in tuberculosis work, they furnish the best method of diagnosis, and even in laboratories devoting much time to tuberculosis they are often necessary for proof of pathogenicity.

## CONCLUSION

It is believed that the combination of tracheal lavage plus culture brings us to a new era in our ability to evaluate properly the clinical status of minimal tuberculous lesions. The technique is sensitive, accurate, rapid, and the procedure of gathering material for examination is simple to perform.

The sensitiveness of these combined techniques is such that we are not yet prepared to use the procedure in evaluation of therapy. At present it is doubtful whether it should be used for this purpose. It is, however, a procedure that is of tremendous help diagnostically in evaluating lesions for which we previously had to depend to a large extent upon our clinical judgment alone.

## CONCLUSIONES

*Empleo Combinado del Lavado Traqueal y de los Cultivos como Procedimiento de  
Diagnostico en la Tuberculosis Pulmonar*

Opina el A. que la combinación del lavado traqueal y de los cultivos nos lleva a una nueva era en nuestra capacidad para justipreciar el estado clínico de las lesiones tuberculosas mínimas. La técnica es delicada, exacta, rápida y el procedimiento para recoger el material para examen es sencillo en su ejecución.

Tan delicadas resultan esas técnicas combinadas que el A. no se siente todavía en aptitud de usar el procedimiento para la valuación de la terapéutica, y duda que deba usarse para ese fin por ahora. No obstante, la técnica posee inmenso valor diagnóstico para justipreciar lesiones en las que antes había que atenerse en gran parte exclusivamente al juicio clínico.

*Acknowledgment*

A considerable portion of the data comparing guinea pigs with egg yolk media and (in his case) liquid Dubos media were obtained from Mr. Jack L. Wallace of the Veterans Administration Hospital in Livermore.

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## AUSCULTATION

### A New Conception of the Respiratory Murmur and Its Place in Diagnosis

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(Received for publication February 3, 1949)

When one suggests the displacement of an established opinion, he should offer a logical substitute. In previous publications (1, 2, 3, 4) the writer made a new appraisal of auscultation based on clinical experience and facts in physics and physiology which have been discovered since Laennec's time. He now wishes to add further evidence to show that the respiratory murmur is composed of sound vibrations which originate in all component parts of the respiratory mechanism, and to point out how this fact may be used advantageously in the physical examination of the lungs.

For more than a century auscultation has been accepted as the chief measure on which dependence can be placed in the physical diagnosis of diseases of the lungs and pleura, and yet, as taught, it is not satisfactory. This is a prime reason why physical diagnosis in chest diseases has been disappointing and why its place has been yielded so willingly to the roentgenogram. On the other hand, could physical examination be satisfactory, the personal element in it should make it an invaluable procedure.

No matter if we are obliged to change our opinion as to the cause of the normal and abnormal respiratory murmurs, this can in no way take away the value of auscultation, or remove from Auenbrugger (5) and Laennec (6) the honor of having founded physical examination of the chest.

Laennec said "The sound of respiration presents different characters, according as it takes place in the pulmonary tissue, the larynx, the trachea, or the large bronchial trunks." He described vesicular respiration thus "a gentle but extremely distinct murmur, which indicates the penetration of air into the pulmonary tissue, and its expulsion." It may be heard best "where the lungs are nearest the surface of the body, namely, the anterior-superior, lateral and posterior-inferior parts."

He designated "as bronchial respiration, the sound produced by inspiration and expiration, in the larynx, trachea, and large bronchial trunks situated at the roots of the lung. After the roots of the lungs, the summits are the parts of these organs where the bronchial respiration is manifested in the most characteristic manner." He practically ignored expiration, but his associates described the length of inspiration to expiration as 10:2.

Beau (7) in 1834 suggested that the respiratory murmur is caused by air passing through the glottis, the sound being transmitted and modified by the bronchi and air cells, as suggested by Laennec.

Textbooks for the past century have almost universally accepted the explanations of the respiratory murmur as given by Laennec and Beau, some being more favorable to Laennec's explanation, others to that of Beau.

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Skoda (8) accepts the cause of the vesicular and bronchial murmur as given by Laennec

Musser (9), in discussing the bronchial murmur, states "The sound is caused by the passage of the air through the nares into the wider pharynx when the mouth is closed, and through the trachea and large bronchial tubes," and states

"The vesicular murmur is produced partly in the finest bronchial tubes and air cells by their expansion and contraction, and partly in the upper air passages, the latter sound being modified on account of the intervention of the air-vesicles between the ear and the larger bronchi "

Guttmann (10) discusses the theory of Beau that the respiratory murmur is due to the sound made by the air passing through the larynx, the bronchi, and air cells, and says that this theory must give way to Laennec's idea that the sound is produced by the air passing through and dilating the bronchi and then the air cells

Da Costa (11) believes that the pulmonary tissue is the principal factor. In discussing the theories of the respiratory murmur arising in the larynx and being transmitted down through the bronchi and air cells, and the theory of Sahh that the local movements of the pulmonary parenchyma account for certain elements in the murmur, he states "Together these two hypotheses serve as a better explanation than the original theory of Laennec that the sound was due to the friction of the air current in the bronchi and infundibuli "

Powell and Hartley (12) state "Laennec was of the opinion that the sounds originated in the affected lung, but it is now admitted that they are in reality generated in the larynx, and thence conducted down the passages into the chest, and so to the observer's ear "

Elmer and Rose (13) are dissatisfied with both Laennec's and Beau's suggestion for the cause of the respiratory murmur and state that the "vesicular murmur is merely bronchial breathing softened in its transmission from the larynx along the aërial column contained in the trachea and bronchi, mingled with the soft crepitation of innumerable pulmonary alveoli during their inflation and subsequent collapse "

It will be seen that none of these authors divorces his idea from the air column and the structures of the upper air passages and the bronchial and pulmonary tissues. All describe the inspiratory murmur as being longer than the expiratory.

These descriptions are not satisfactory, nor are they in accordance with present knowledge. They must be studied further to make them most useful. The physician who practices at the bedside should develop his ability to see, hear, and feel the signs of disease which the patient presents. It is necessary for him to make himself as independent as possible of roentgenographic examination because it is not always available. Any knowledge that will make physical diagnosis more useful is to be desired. The following discussion of auscultation and the respiratory murmur is offered with this in mind.

During the writer's more than fifty years of examining chests, he has made certain observations which are contrary to these teachings and which he believes will make auscultation more useful.

It is evident to anyone who will examine carefully that, normally, inspiration is not longer than expiration—10 2, 5 3, 3 1, et cetera, as taught, but actually shorter.

The weakness of the respiratory murmur in case of abdominal breathing indicates that the air column passing through the larynx and bronchi and expanding the air cells cannot be the origin of the respiratory sounds, for the air enters the

air passages the same as it does in the usual type of breathing, yet the murmur is weak. We also have a respiratory murmur when the larynx is by-passed by the bronchoscope.

Moreover, it is not rational to accept without questioning that the murmur heard near the hilum and in the interscapular region is produced, even chiefly, by the air as it passes the glottis, enters and dilates the bronchi, impinging on their surfaces, and that in the main portion of the lung, by air entering and dilating air cells.

*Relation of respiratory murmur to respiratory mechanism.* What may we offer as a substitute for these long held opinions? After noting that inspiration is not longer than expiration, the writer was next impressed with the fact that there is a muscular element in the murmur (14). By placing the stethoscope over a contracting biceps, a sound was heard which possessed some of the qualities of the respiratory murmur. It was noted during normal breathing that a fairly good but weak murmur could be heard over the abdominal muscles. A murmur was also noted over the chest wall where the lungs were collapsed by pneumothorax and the lung tissue was separated widely from the chest wall by an air cushion. Such murmurs are usually weak if the pressure is marked, but sometimes, when the parietal pleura is thickened, they may not be far from normal in their intensity, indicating that different factors enter into their production. The thickness of the pleura alters the murmur, sometimes increasing and sometimes decreasing it. More recently a weak respiratory murmur was heard over the chest wall where the lung had been removed by pneumonectomy. Surely the entry of air could not be responsible for this sound because the pulmonary elements with the air current had been removed from the side.

To what can the sounds be attributed in pneumothorax and pneumonectomy, where a little air may enter in the one case, and none in the other? On careful analysis the answer seems evident. The respiratory murmur begins with the inspiratory movement and ends with the adjustment of the pulmonary tissues at the end of the expiratory movement. Is it not reasonable then to attribute the murmur to the respiratory mechanism, every part that causes and transmits sound vibrations, the muscles, the bony cage, the pleura when inflamed or thickened, the mediastinum especially when pathological, the bronchi, the pulmonary tissue, the air passages, and the column of air?

It seems rational to look upon the air column and air spaces as incidental rather than the chief factors in the production of the respiratory murmur. The force of the tidal air as it enters the lungs is nullified by the residual air already present, and the air after entering the large bronchi diffuses into the small bronchi and alveoli when the thorax is enlarged and is expressed during the contraction of the thorax.

That part of the respiratory mechanism which is responsible for the *bronchial murmur* is normally limited to the superior portion of the chest and is most distinct posteriorly. Here the sound vibrations are produced by the air current, the larger bronchi, a comparatively small amount of pulmonary tissue, a heavy musculature, and the least elastic portion of the bony cage.

On the other hand, that part of the respiratory mechanism which is largely



responsible for the *vesicular murmur* is dominant in the anterolateral and lower portions of the lungs. Here the murmur is composed of vibrations which originate in structures largely air-containing (the finer bronchi and air cells) plus a limited musculature and an elastic bony cage.

In auscultation of the normal lung and pleura, we are listening to the complex sound caused by vibrations in the respiratory mechanism in action, and in pathological conditions, we hear that modification of the normal sounds which the particular pathological process causes in the action of the respiratory mechanism. No other explanation seems adequate to account for the variations in the respiratory murmur which are met in diseases of the lungs and pleura. Infiltration decreases the proportion of air-containing elements, which produce sound vibration, and disturbs the action of the respiratory mechanism.

Moreover, in the sounds heard on auscultation it is evident that there are two distinct factors which must be taken into consideration—sound production and sound transmission. Sometimes one is predominant, and again, the other. The respiratory murmur heard at any given point consists of a composite sound originating in that portion of the respiratory mechanism which is transmitted to the ear at the point of observation.

Infiltrations in the lung alter respiratory movement and according to their nature, size, density and location, change the sounds. They act in two ways.

First, acute inflammatory processes such as active tuberculosis cause spasm of apical muscles, particularly the sternocleidomastoid, scaleni, levator anguli scapulae and acromial portion of the trapezius above, and the crus and central tendon of the diaphragm below, and modify respiration by reflexly lessening the movement of the hemithorax in which the pathological process is located (15, 16, 17).

Second, all infiltrations, whether inflammatory or noninflammatory, interfere with full respiratory movement by their presence, the amount of interference varying with the extent and character of the infiltration. They also modify sound transmission.

It readily can be seen that the effect of both the reflex and the infiltration *per se* is to slow and lessen both the inspiratory and expiratory movement. This alters the sound vibrations. It prolongs both phases of the respiratory murmur and in many instances produces a higher-pitched note. If the infiltration results in much fibrosis, then the murmur may show the above disturbances to a high degree and be transmitted with increased force. Thus we see in the increased voice transmission caused by extensive scar tissue in tuberculosis, particularly when situated near the apex, or in a cavity with smooth walls surrounded by dense scar tissue—the *pectoriloquy* of Laennec.

The respiratory murmur may have different qualities according to the individual chest, the part of the chest in which the infiltration is located, and the particular characteristics of the infiltration. All of these factors will influence respiratory movement differently. One rarely finds a markedly harsh murmur or marked voice transmission when the infiltration is small, scattered, or situated deep in the lung surrounded on all sides by functioning pulmonary tissue, no matter what the characteristics of the pathologic process. If the infiltration is small, the

respiratory mechanism may be influenced so little that the presence of the pathology may be wholly overlooked on auscultation

Emphysema, such as we find in chronic bronchitis, bronchiectasis, asthma, or the compensatory emphysema found in chronic, far advanced tuberculosis, changes the respiratory movement and the accompanying murmur according to the following pattern which varies according to the degree of emphysema present. The lungs at rest are dilated, the intercostal spaces are distended, the bony cage is fixed and rigid, and the diaphragm is depressed and incapable of full movement. Every factor which enters into normal respiratory movement is limited in its activity, hence the respiratory murmur is weak.

In pneumothorax, the auscultatory sounds consist partly of the weak contraction of the chest muscles and those made by the feeble movements of the bony cage, plus whatever pulmonary tissue there is to engage in the respiratory movement. In pneumonectomy the stretching of the tissues which occupy the former lung space in response to respiratory effort may produce detectable sound vibrations.

In a chronically contracted lung the pulmonary, the muscular, and the bony cage elements of the respiratory murmur may or may not be largely removed and the sounds vary accordingly. But if there is marked fibrosis or a cavity in the midst of dense scar and the air freely enters, the vocal sounds may be strongly transmitted. This is *bronchophony* and *pectoriloquy*, in which transmission greatly overshadows sound production.

Diseases of the pleura may also alter the respiratory movement and change the respiratory murmur. Acute pleuritis causes local spasm of the intercostal muscles and reduces the movement of that segment of the bony cage over the part of the pleura which is inflamed, causing a decrease in the intensity of the murmur. It also may cause a friction rub when the inflamed surfaces move on each other. Should an effusion occur, the nature of the sounds will depend on the amount of fluid present. Much fluid distends the intercostal spaces, reduces the movement of the muscles and bony cage, separates the pulmonary tissue from the parietal pleura, and lessens the respiratory sounds.

*Rales and the respiratory mechanism.* Rales may be heard in pathological conditions of both the lungs and pleura. They are called *crepitant*, *subcrepitant*, *gurgling*, and *musical*. Roughly speaking, the first three varieties are considered to be caused by mucus in the bronchi, air cells, and cavities, while the musical rale is an obstructive rale caused by partial blocking of a bronchus. But there are pleural rales which cannot be distinguished from nonmusical rales of pulmonary origin.

The writer knows of no sure way to differentiate the fine and moderately coarse rales originating in the lung from those originating in the pleura. Both may be heard on deep inspiration and on expiration followed by cough and a quick inspiration, and both may now and then be heard on both inspiration and expiration.

The best evidence for differentiating these rales depends on the pulmonary and pleural reflexes, and this is not wholly satisfactory.

If atrophy of the subcutaneous tissue is present and does not extend below

the second rib anteriorly and the spine of the scapula posteriorly, rales heard are most likely of pulmonary origin, because this is the area of the pulmonary trophic reflex.

If atrophy is found anywhere between the second rib anteriorly and the spine of the scapula posteriorly above, and the lower margin of the ribs, this shows that the pleura has been inflamed and as a result the intercostal (18) and subcutaneous tissues (3) are degenerated and rales heard over these areas are likely to be of pleural origin. The fact that sometimes rales are not heard does not mean that no pathology is present.

When the trophic reflex extends from the apex down below the second rib anteriorly and the spine of the scapula posteriorly, rales are uncertain as to origin, for this indicates that both pulmonary and pleural tissues have been involved.

After inflammation of the pleura has subsided, or an effusion has become absorbed, the overlying intercostal and subcutaneous tissues may be permanently degenerated and alteration of the respiratory movement and murmur may persist. Degeneration of the subcutaneous and intercostal tissues with alteration of the murmur frequently follows the thickening of the parietal pleura caused by the irritation of the air in case of pneumothorax treatment. In some of these cases, rales are found and occasionally pain is present. Detectable atrophy is nearly always present if the pneumothorax has been maintained for more than a few months.

Rales arising in both the pulmonary tissues and the pleura may be persistent, and pleural rales may be permanent. I have heard these rales on re-examining patients nearly fifty years after I first noticed them.

It is not at all uncommon for the movement of the chest wall, hence the respiratory murmur, to be perceptibly lessened if the previous pleural involvement was extensive.

Pain may recur years after the acute phase of the pleurisy has passed, especially under conditions of low energy, tiring, emotional stress, worry and disappointment, menstruation, and changes in weather.

*Constructive suggestions.* This discussion of auscultation is not wholly destructive. There is a constructive side. It attempts to show what the respiratory murmur is not, and also what it is. This discussion takes away much of the independent value heretofore ascribed to auscultation and shows that all methods of physical examination of the lungs and pleura are interdependent. It raises auscultation from its dependence on the erroneous belief that the respiratory murmur is caused by the rush of air into the bronchi and air cells, and gives as its basis vibrations arising in the respiratory mechanism.

With this new conception the so-called *vascular murmur* is heard in the anterosuperior, lateral, and lower portion of the lung, where the pulmonary tissues are dominant in the production of sound vibrations, and the so-called *bronchial murmur*, in the higher area and the posterosuperior portion, where the nonpulmonary tissues are dominant, as has long been taught. Infiltrations, no matter where located, reduce the dominance of the vibrations from the pulmonary tissue and make the sounds take on what Laennec called a *bronchial* quality.

The terms *bronchial* and *vesicular* may be retained but they should be assigned to the entire respiratory mechanism and carry the new meaning of dominance in non air-containing tissues in the production and transmission of the *bronchial murmur*, and dominance in the air-containing tissues in the *vesicular murmur*

By carefully inspecting and palpating chests, the examiner may determine with fair definiteness how the respiratory mechanism is disturbed. He should pay due regard to the reflex spasms and degenerations caused by pathological changes in both lungs and pleura, and also note the effect on both the form and movement of the chest caused by infiltration and other pathological changes. Prominent among these are emphysema, rigid thorax, and marked contraction, which are often evident to the eye and more fully determined by palpation and percussion. If he will make these initial observations he will have some idea of what the respiratory murmur may be before putting a stethoscope on the chest. However, he must not expect to find the same sounds caused by the same pathology in all chests. We have been taught to expect to find far greater changes in the murmur than are present, especially where infiltrations are small or widely scattered. It is surprising to find how often they are so slight as to be almost unrecognizable.

The examiner must make more of physical examination of the chest than the use of auscultation and percussion. It must mean a complete and careful study of the patient's respiratory mechanism. Seeing and feeling are of equal importance to hearing. Disturbed physiology, as shown in the reflexes and in interference with the respiratory mechanism, which may be determined by inspection and palpation, take on added importance and must be utilized in order to obtain a full picture of any disease affecting either the lungs or pleura. Physical examination must be rewritten with due emphasis on the utilization of all data obtained on sight, touch, and hearing, rather than limiting it to what is heard through the stethoscope and determined by the use of the percussing finger.

#### SUMMARY

The respiratory murmur cannot be due to the air rushing through the larynx and impinging on the bronchial walls and dilating the air cells, because the lungs always contain residual air which stops the force of the incoming current and causes the air to enter the finer bronchi and air cells by diffusion.

The respiratory murmur consists of a mixture of sound vibrations originating in all components of the respiratory mechanism.

The sound vibrations which cause the *vesicular murmur* originate in the respiratory mechanism in the anterior, lateral, and lower portions of the chest where the air cells predominate, the musculature is light, and the bony cage elastic.

That part of the respiratory mechanism which normally causes the *bronchial murmur* is found in the superior portion of the chest and is most distinct posteriorly. Here the sound vibrations are produced by the air current, the larger bronchi, a comparatively small amount of pulmonary tissue and air cells, a heavy musculature, and the least elastic portion of the bony cage.

The importance of the trophic reflexes in the differentiation of pulmonary and pleural rales is discussed

One should begin examination by inspection and palpation. By these measures he determines the shape, deformities, and movements of the chest and whether or not any reflexes or any departures from the normal are present. With this information he may proceed to percussion and auscultation more intelligently and with greater confidence and understanding

#### SUMARIO

#### *La Auscultación Nuevo Concepto del Sopro Respiratorio y de su Puesto en el Diagnóstico*

El sopro respiratorio no puede deberse al rápido paso del aire por la laringe, chocando después contra las paredes bronquiales y dilatando las células aéreas, porque los pulmones contienen siempre aire residual que atenúa la fuerza de la corriente de entrada y hace que el aire penetre por difusión en los bronquios más delicados y en las células aéreas

El sopro respiratorio consta de una mezcla de vibraciones sonoras procedentes de todas las partes componentes del mecanismo de la respiración

Las vibraciones que ocasionan el *sopro vesicular* tienen su origen en el mecanismo respiratorio de las porciones anterior, lateral e inferior del torax en las que predominan las células aéreas, la musculatura es liviana y la caja ósea elástica

La porción del mecanismo respiratorio que ocasiona normalmente el *sopro bronquial* radica en la porción superior del torax, hallándose más en evidencia en la región posterior y produciendo allí las vibraciones sonoras la corriente de aire, los bronquios mayores, una proporción comparativamente pequeña, de tejido pulmonar, una musculatura pesada y la porción menos elástica de la caja ósea

Discutese la importancia que revisten los reflejos tróficos en la diferenciación de los estertores pulmonares y pleurales

El examen debe comenzar con la inspección y la palpación que permiten determinar la conformación, deformidades y movimientos del tórax y si existen reflejos o desviaciones de lo normal. Con esta información, puede pasarse entonces a la percusión y la auscultación en forma más inteligente y con mayor confianza y comprensión

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# Case Reports

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## TREATMENT OF ACUTE OBSTRUCTIVE TUBERCULOUS ENTEROCOLITIS BY "NONSURGICAL ILEOSTOMY" AND STREPTOMYCIN<sup>1 2</sup>

A Case Report

JOHN W. WOODBURY AND SAMUEL PHILLIPS

(Received for publication May 2, 1949)

Although acute obstruction is considered to be a rare complication of tuberculous enterocolitis (1), it is one of the most serious (2). When it occurs, effective treatment is often impossible (1). The following case report includes several unusual aspects but is primarily presented to illustrate a successful method of treating this complication.

### CASE REPORT

L. L. C., a 23-year-old white male veteran, first came under our care because of acute tuberculous tonsillitis. The patient had become permanently and totally paraplegic with a "sensory level" at D 5 when his spine and left chest were traversed by a rifle bullet in 1945. He had received surgical, genitourinary and paraplegic attention, and plastic surgery, not as yet completed, for the closure of decubitus ulcers. He was in good nutritional state and free of significant genitourinary infection.

On December 7, 1946, this patient developed a sore throat, followed by nausea, vomiting, diarrhea, severe toxicity, and irregular fever up to 103°F. His tonsils were enlarged and acutely inflamed and within five days exhibited areas of ulceration covered with greyish exudate. There was no significant cervical adenopathy. The patient was investigated and treated energetically with sulfonamides and penicillin without response. In the middle of January 1947, repeated smears from the tonsils showed acid-fast bacilli, subsequently found by culture and animal inoculation to be virulent human tubercle bacilli. Several specimens of sputum and a single stool were also positive for these microorganisms. Chest roentgenograms revealed merely the residual scarring from his old gun-shot wound (figure 1). The patient was given streptomycin, 0.4 Gm intramuscularly every four hours for seven days and made a very prompt and dramatic recovery.

The sputum, however, remained positive for acid-fast bacilli on smear through March 1947, and even thereafter was intermittently positive for *M. tuberculosis* on culture. Bronchoscopy was performed in April but failed to reveal any tracheobronchial disease. The patient was kept on bed rest and he appeared clinically to be doing well except for occasional brief episodes of diarrhea and low-grade fever, which are not uncommon in most paraplegics. In November 1947, his diarrhea became persistent and the stools exceedingly foul. Hyperpyrexia and leukocytosis were present. The stools were consistently positive on smear and culture for tubercle bacilli. Physical examination at this time revealed that the colon was palpable as an indurated tube from cecum to sigmoid. An ulcerated, macerated, granulomatous mass involving the posterior segment of the anus was also found. Proctoscopy revealed that this mass extended 3 to 4 cm up the posterior wall of the rectum. Biopsy was taken and revealed tuberculous granulation tissue.

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<sup>1</sup> From the Tuberculosis Section Medical Service, Veterans Administration Medical Teaching Group, Kennedy Hospital, Memphis 15, Tennessee.

<sup>2</sup> Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

Upper gastrointestinal series and small intestinal roentgenograms were reported negative. A barium enema on December 10, 1947 demonstrated gross alterations of the colon from the cecum to splenic flexure, with loss of flexibility, reduction of lumen, and irregular, granulated borders of the barium column (figure 2). The cecum appeared most involved. Similar changes were apparent in the last 12 inches of the terminal ileum.

On December 16, 1947, 0.5 Gm. of streptomycin twice daily was started, at first orally. Because there was no apparent effect on either the patient's fever, foul smelling diarrhea, or general condition, the oral route was discontinued on December 31, 1947 and replaced by 0.5 Gm. of streptomycin twice daily by the intramuscular route which was continued for a total of 120 days.



FIG. 1. Chest roentgenogram November 7, 1947 at time of onset of gastrointestinal symptoms. No evidence of active tuberculosis.

On January 2, 1948 the patient suddenly developed acute lower bowel obstruction with right lower quadrant cramp-like pain, abdominal distension, nausea, and vomiting which soon became fecal in character. Relief was afforded quite promptly by Wangensteen drainage of the stomach and the use of parenteral fluids. During January 1948, however, on five separate occasions there occurred similar episodes of obstruction. All were treated in the same fashion with the result that the patient would retain liquid foods and be able to pass feces normally for three to seven days before obstruction would occur.

In spite of the utmost efforts to maintain the patient's nutrition and the employment of intravenous glucose and protein hydrolysates, the patient's weight dropped from 126 pounds to 112 in thirty days. Consultation with the surgeons confirmed the opinion of all concerned that in the presence of such widespread tuberculous enterocolitis, surgical intervention was inadvisable.



On February 4, 1948 a Miller Abbott tube was passed down to the distal portion of the ileum and a constant Wangensteen suction was maintained for fourteen days (figure 3). The patient was fed a low residue liquid diet by mouth with a few low-residue solids, supplemented by a quart of high caloric milk formula per day.<sup>3</sup> This regimen was designed to maintain the patient's caloric and protein requirements by normal alimentation. At the same time it was hoped to prevent further episodes of obstruction by diverting the fecal stream from the terminal ileum back up through the Miller-Abbott tube by means of the Wangensteen suction. Consultation with our gastroenterologist for his opinion of the

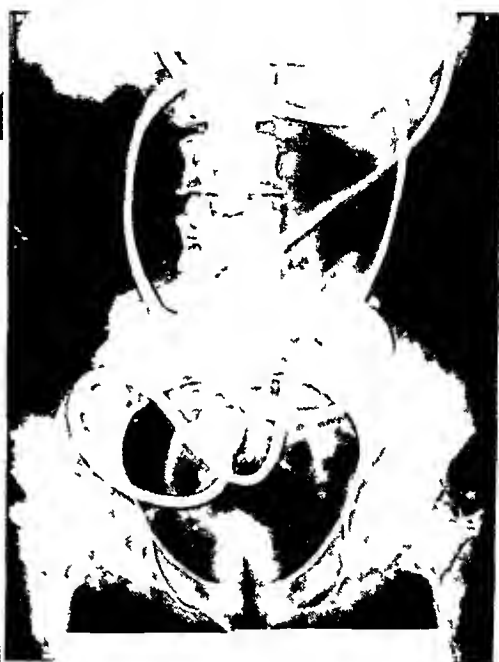


FIG 2 (Left) Barium enema, December 10, 1947 showing marked involvement of ileum (lower arrow), ileocecal area (middle arrow), and ascending and transverse colon (upper arrow)

FIG 3 (Right) Miller Abbott tube within the ileum

method led to our discovery that a report had just been published by Michelli and Miller (3) on the use of the Miller-Abbott tube for similar purpose in the treatment of idiopathic ulcerative colitis. They had termed the method "Medical Ileostomy."

<sup>3</sup> Formula employed

INGREDIENTS		MEASURE	C	P	F	CALORIFS
Skim milk	500 cc	1 pt	25	17	1	180
Powdered skim milk	200 Gm	2 c	106	72	2	718
Karo	100 Gm	$\frac{1}{2}$ c	73	—	—	292
Eggs		2	—	14	12	164
Lactose	100 Gm	1 c	100	—	—	400
Milk	250 cc	$\frac{1}{2}$ pt	12	8	10	170
Chocolate syrup	100 Gm	$\frac{1}{2}$ c	70	0.6	5	321
Total (approximate)	1110 cc	38 oz	386	111.6	30	2,245

In our patient 200 to 2,000 cc. of liquid fecal material was obtained daily through the Miller-Abbott tube. The patient was perfectly comfortable during this period and there was no recurrence of symptoms of obstruction. Four days after withdrawal of the tube, however,



FIG. 1 (Top) Barium enema, April 23, 1948 following conclusion of therapy. The ileum appears improved although markedly dilated (lower arrow). The involved ascending and transverse colon has regained normal appearance (upper arrow). In between is the residual deformity and marked constriction in the barely visible cecum (middle arrow).

FIG. 5 (Bottom) Autopsy specimen of cecum, showing marked fibrosis and constriction.

symptoms reappeared, necessitating the reinsertion of the tube for another period of fourteen days. When the tube was finally withdrawn on March 8, 1948 there was no further clinical obstruction. During the month in which the patient had remained on the described

regimen, he regained 9 pounds of the weight he had lost. He was then able to take a high caloric low residue diet without difficulty and by April 27, 1948 his weight had increased to 137 pounds, representing a 25 pound weight gain and the best weight he had been able to attain since he had become paraplegic.

In the meantime, intramuscular streptomycin therapy had been continued with disappearance of fever and diarrhea. At cessation of this therapy the rectal granulomatous mass had shrunk to 2 cm., and a barium enema performed at this time demonstrated marked improvement of terminal ileum and transverse colon with return of normal mucosal pattern, mobility, and flexibility (figure 4). The cecum and ascending colon still showed gross changes with marked stenosis of the lumen immediately above the cecum to a diameter of 5 mm. The stools were still positive for tubercle bacilli and these were found to be resistant to streptomycin.

The question of surgery arose at this time. It was the opinion of the surgeons that because of the very recent widespread involvement of the colon resection (4, 5) of the residual constricted portion would not be without hazard of reactivation. They also felt that since the patient was improving so remarkably on the medical regimen there was no urgency and that it would be wise to wait until a definite period of stability had been attained.

The patient continued to improve in every way until approximately three months after conclusion of the course of streptomycin and more than four months after the withdrawal of the Miller Abbott tube. On July 20, 1948 he complained of headache. It soon became only too obvious that the patient had developed tuberculous meningitis. The cerebrospinal fluid was under increased pressure, contained 124 leukocytes with 90 per cent lymphocytes and the values for sugar and chlorides were low. He went downhill very rapidly and expired August 9, 1948.

Gross findings at autopsy showed the ileocecal area to be a mass of cicatricial tissue in which the appendix was incorporated. The ileocecal junction was so constricted that it would allow the passage of only a thin probe (figure 5). The mucosa of the cecum in this area was red, thickened, and showed several elliptical areas of ulceration measuring 0.2 to 0.5 cm. in longest diameter. The rest of the bowel and the regional mesenteric nodes appeared normal.

The lungs, in spite of a very careful examination, revealed merely a discrete caseoelastic nodule 1.0 cm. in diameter, at the extreme right apex, and a similar nodule, 0.5 cm. in diameter, in the region of the right hilum. The tracheobronchial nodes appeared normal.

The tonsils were removed and appeared normal on gross examination. Unfortunately they were lost before they could be examined by microscopic section. The remaining abdominal viscera showed no evidence of tuberculosis. Permission for examination of the brain could not be obtained. However, a portion of the cervical area of the spinal cord was removed.

Microscopic examination of the lungs was negative except for some patchy areas of atelectasis. The spinal cord showed the subarachnoid space to be filled by an exudate of fibrin, and collections of epithelioid and chronic inflammatory cells involving the pia and blood vessels. The sections from the ileocecal region showed the epithelial lining of the mucosa to be denuded, with some glandular crypts remaining. The tumor proper was thickened by fibrosis and chronic inflammatory cells. The submucosa showed dense fibrosis and chronic inflammation. Scattered throughout the muscularis and serosa were a number of characteristic tubercles.

Although tuberculous enterocolitis is usually associated with progressive, far advanced pulmonary tuberculosis (6, 7), cases of so called "primary" involvement, where no active pulmonary lesion is present, are described (1, 5, 8, 9). A distinctive feature in this case was that the presence of tuberculosis first became manifest through the development of acute tuberculous tonsillitis. The late recognition of the enterocolitis was undoubtedly related to the patient's paraplegia.

This case demonstrates the relief of obstruction and the maintenance of a patient's nutrition at optimal levels by the use of "nonsurgical ileostomy." By the same means, time was made available for marked resolution of the underlying tuberculous disease by streptomycin. Whether excision of the ileocecal area would have been possible if the patient had not subsequently developed meningitis was not, of course, answered. From the appearance of the bowel at autopsy, however, it was believed that such surgery would have become possible.

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# A CASE OF MASSIVE HEMOTHORAX COMPLICATING THERAPEUTIC PNEUMOTHORAX

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## REVIEW OF LITERATURE

Hemothorax and hemopneumothorax have occasioned much interest recently because of their frequent occurrence as a result of chest injuries received during World War II. The chief complication to be feared was found to be that of fibrothorax. T. Simpson (1) and A. F. Jones (2), in their series of cases, advise early aspiration and re-expansion, the latter author having performed thoracotomy with evacuation of the clot and decortication in 38 cases to prevent this development.

The spontaneous occurrence of hemothorax and hemopneumothorax is also not unusual. Two of the earliest reports were those of fatal hemopneumothorax cases described in 1900 by Rolleston (3) and Pitt (4). In the former, sixty ounces of blood were found post mortem in the intrapleural space and no source of hemorrhage could be located. In the latter, there were eight pints of unclotted blood in the pleural cavity while near the apex was an emphysematous bulla attached to which was a torn fibrous band. However, again no patent vessel could be found. There was no evidence of tuberculosis in either case. During subsequent years numerous other cases have been reported. In 1937, H. U. Hopkins (5) summarized the literature concerning hemothorax, which included 46 cases, and added 3 of his own. This included 4 patients with artificial pneumothorax in whom intrapleural hemorrhage had occurred. One of the latter was that described by Heise and Krius (6) in 1920 and will be referred to again later. E. Korol (7), in his article on hemopneumothorax and hemorrhagic pleurisy, includes 130 cases, 30 of which occurred during artificial pneumothorax therapy, but he does not distinguish between frank blood and merely blood-tinged fluid. Jones and Gilbert (8) also discuss spontaneous hemopneumothorax and add a case of their own in which death occurred from circulatory obstruction, autopsy disclosing a thick layer of fibrin on both lung and pleura. There were 4,000 cc of blood and 750 cc of free fibrin in the pleural space and marked dilatation of the inferior vena cava and the renal and portal veins. The cause in this case was an emphysematous bleb, but the actual site of the hemorrhage was not found.

Subsequent reports include those of Bernstein, Klosk, and Parsonnet (9), A. F. Jennings (10), and Prym and Lief (11). A case of spontaneous hemopneumothorax was also treated at the Kingston Veterans Hospital with repeated aspirations and subsequent re-expansion of the lung. There was no evidence of pulmonary disease.

Hemothorax occurring during the course of artificial pneumothorax must be a rare condition. The case described by Heise and Krius (6) in 1920 followed the initial refill in a far advanced case of tuberculosis, and the patient died fourteen hours after the onset of symptoms. Autopsy disclosed 2,000 cc of blood in the pleural cavity, a small hole overlying a cavity and situated near a thick adhesion was apparently the site of the bleeding vessel, but no actual bleeding point could be found. The lung itself was cretaceous throughout, with numerous cavities. W. L. Meyer (12) describes a case believed to be a consequence of damage to the intercostal vessels during a refill. A total of about 2,100 cc of

<sup>1</sup> From the Kingston Veterans Hospital, Department of Veterans Affairs, Kingston, Ontario, Canada.

blood were aspirated (1,700 cc on one occasion) from the pleural cavity in this case. Subsequent progress was satisfactory and the pneumothorax was continued. Other than this latter report, no cases could be found in the literature of recent years. As mentioned earlier, H. U. Hopkins (5) refers to 3 other similar cases and E. Korol (7) to 30 cases, but neither states in how many there was frank hemorrhage. The reports of these cases were not available for further information. C. B. Hogg (13) refers to the puncture of a large vessel occurring during artificial pneumothorax and Puffitt and Crombie (14) also describe a similar occurrence, but in neither case was there the resultant complication of hemothorax.

#### CASE REPORT

J. L., a 25-year-old ex-prizefighter, was admitted to the Kingston Veterans Hospital on February 6, 1946. A left-sided chest pain of one week's duration was followed by a gross hemoptysis of approximately 120 cc twenty-four hours prior to admission. Physical examination revealed no abnormalities. On a chest roentgenogram a 2.0 cm cavity opposite the third rib on the left in the region of the hilum could be seen. This contained a fluid level. The lesion had been less prominent but overlooked in the discharge film taken January 9, 1946. Sputum was positive for acid-fast bacilli on direct smear. The erythrocyte sedimentation rate was 11 mm in one hour.

Because of roentgenographic evidence of cavity closure and temporary "conversion" of sputum, artificial pneumothorax was not commenced until September 13, 1946, when a sputum specimen of July 1946 was reported positive for *M. tuberculosis* following eight weeks' culture. Subsequent progress was uneventful until the night of November 26, 1946. Fluoroscopic and roentgenographic examinations disclosed a satisfactory pneumothorax. A film taken October 30, showed a 50 to 60 per cent degree of collapse following a refill and no adhesions were evident (figure 1). Refills were being given at seven-day intervals and pressure readings were satisfactory, the initial reading averaging  $-7$   $-4$  and the final reading averaging  $-3$   $-0$  cm of water.

On the morning of November 26, the usual refill of 500 cc was given. The initial reading was  $-6$   $-3$  and the final  $-3$   $-0$  cm of water. Fluoroscopic examination revealed a 70 per cent degree of collapse and no fluid was present. At about 6 p.m. the same day, the patient complained of slight tightness in the chest. There was possibly a slightly greater degree of collapse but nothing unusual was noted. At bedtime there was only slight discomfort. At midnight he began to hiccough and slept only sporadically. At 9 a.m. he was acutely short of breath, pale, and most distressed because of severe and constant hiccoughing, which had apparently only recently become severe. Fluoroscopic examination revealed marked shifting of the heart and mediastinum towards the right, the collapse now amounted to 80 to 85 per cent, and a small amount of fluid obliterated the costophrenic angle. The intrapleural pressure reading was greater than the height of the manometer scale, i.e., greater than 20 cm of water positive pressure. Seven hundred cubic centimeters of air were removed and the final reading thereafter was  $-6$   $+1$ . The procedure was followed by marked relief. Four hours later the dyspnea and hiccoughing returned and 500 cc of air were aspirated. The initial reading was  $+5$   $+10$  and again the patient was relieved. Suddenly, about 5 p.m., marked shock, pallor, and cyanosis developed, with profuse sweating and tracheal deviation. Nausea and vomiting were also severe. The dyspnea was not so marked as previously. The possibility of hemorrhage was immediately considered. Physical examination of the chest revealed flatness posteriorly and there was marked shifting of the mediastinum to the right, the heart sounds only being heard to the right of the sternum. Diagnostic aspiration was productive of blood, the hemoglobin level of the peripheral blood had fallen to 10 Gm per 100 cc and a portable roentgenogram of the chest disclosed the fluid level to be opposite the sixth dorsal vertebra. The blood pressure (mm of mercury) was 90 systolic, 70 diastolic. The clinical evidence of shock rapidly grew more severe. It

was obvious that further hemorrhage was occurring and that urgent measures were necessary to save his life

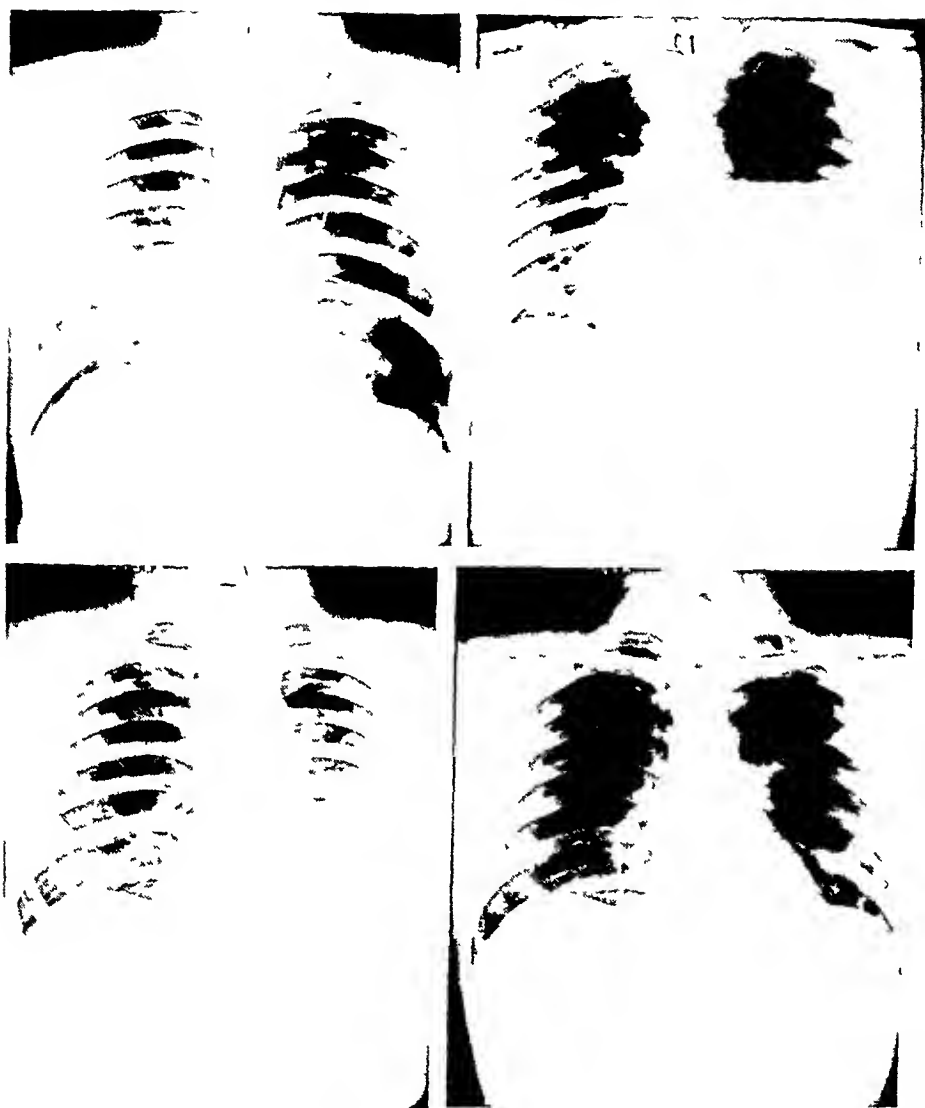


FIG 1 (Upper left) Roentgenogram of the chest one month before massive hemorrhage into the pneumothorax space. No adhesion visualized.

FIG 2 (Upper right) Roentgenogram of the chest on the day after hemorrhage showing fluid level and marked shift of mediastinal structures.

FIG 3 (Lower left) Roentgenogram of the chest five weeks after hemorrhage, showing complete re-expansion of the lung. Pleural clouding still evident.

FIG 4 (Lower right) Roentgenogram of the chest five months after hemorrhage. There is almost no residual pleural change.

The immediate treatment consisted of the following procedures:

Blood was obtained from the blood bank, in the meantime, 500 cc of normal saline were administered. The patient was then given four transfusions of 400 cc, 300 cc, 425 cc, and

400 cc of whole blood (a total of 1,525 cc during the night), as well as 100 cc of 10 per cent glucose in distilled water. At 10 p m a second portable film disclosed no change in the fluid level and it was decided that the hemorrhage had probably ceased. The clinical condition had also improved somewhat, although shock was still quite pronounced. Blood pressure was 90 systolic, 70 diastolic. By 11 45 p m, however, there was a distinct improvement and the blood pressure was now 106 systolic, 80 diastolic. The hemoglobin level had risen to 12 Gm per 100 cc.

On the following morning, the patient was much better and the hemoglobin level was 13.5 Gm per 100 cc. An aspiration was carried out in the eighth interspace at the midaxillary line and 1,300 cc of dark red blood were aspirated without difficulty. The patient felt more comfortable and finally became free of nausea and vomiting, so that the intravenous administration of fluids was discontinued. The fluid level in the chest remained about the same, but the heart sounds could now be heard to the left of the sternum. A portable film confirmed the shift of the mediastinal structures, and disclosed the fluid level at the height of the seventh dorsal vertebra as compared with the sixth dorsal vertebra level of the film ten hours previously (figure 2). No further blood was removed then for fear of precipitating further hemorrhage.

The patient's subsequent progress was satisfactory. A temporary leukocytosis of 18,000 cells per cu mm on the day of the hemorrhage had decreased to 10,500 on the next day. Subsequent leukocyte counts were normal. The erythrocyte sedimentation rate was elevated to 97 mm on December 1, but dropped to 13 mm by December 13. A fever of 100° to 102°F persisted for four days. Penicillin was administered both intramuscularly and intrapleurally.

The results of further aspirations were as follows:

November 27	1,300 cc bloody fluid
November 28	600 cc bloody fluid
November 30	500 cc bloody fluid
December 1	600 cc bloody fluid
December 2 a m	600 cc bloody fluid
December 2 p m	400 cc bloody fluid
December 3	200 cc bloody fluid
December 5	150 cc dark bloody fluid
December 7	150 cc dark brown fluid
December 10	200 cc dark serous fluid
December 11	80 cc dark serous fluid
December 14	0 cc
December 16	115 cc dark serous fluid
December 19	135 cc dark serous fluid
December 21	100 cc dark brown fluid
December 23	100 cc dark brown fluid
December 26	45 cc dark fluid
December 30	65 cc dark yellow fluid
January 3	0 cc
Total	5,340 cc

The heart and mediastinal structures gradually resumed their normal positions, and the lung had undergone full re-expansion by January 3, 1947 (figure 3). The residual pleural clouding decreased steadily thereafter. In the film of April 14, 1947 almost no pleural changes can be detected (figure 4), while that of October 16, 1947 reveals obliteration of the costophrenic angle as the only finding. The physical findings on examination of the chest have also returned to normal. Fluoroscopy disclosed moderate mobility of the left diaphragmatic dome, successive sputum examinations have been negative for tubercle bacilli on culture, and tomographic series failed to reveal evidence of cavity formation. It is therefore to be hoped that the original parenchymal lesion will remain under control.



## COMMENT

The possible sources of the hemorrhage in this patient could have been the following

- (1) Puncture of the lung by the pneumothorax needle This is considered unlikely as there was good collapse before the refill

- (2) Injury to the intercostal vessels as in Meyer's (12) case This is considered to be unlikely because the dyspnea preceded the hemorrhage by some hours

- (3) Rupture of a vesicle on the surface of the lung

- (4) Tearing of a vascular adhesion

It is thought that the last named is the most likely explanation in spite of the fact that no adhesion was visualized roentgenographically In the case described by Heise and Kraus (6), autopsy disclosed a hole in a thinned-out area overlying a cavity and situated near a thick adhesion which had torn In this case there was no such disease in the lung parenchyma, and the hemorrhage would probably have to be attributed to bleeding from the parietal stump of a torn adhesion

As to treatment of hemothorax, most authorities are in agreement that following the period of actual hemorrhage the blood should be aspirated as soon as possible to prevent the development of a fibrothorax (1, 2, 5, 6, 7, 8, 9, 10) Though blood does not clot in an uninfected pleural cavity, the fibrin does settle out and may leave a thick shaggy layer on the surface of both lung and parietal pleura

Therefore, it was decided that the blood from this patient's chest should be aspirated frequently Also, it was considered that the pneumothorax should be abandoned, as the danger of the development of unexpandable lung with fibrothorax was felt to be so great Moreover, the possibility of the further occurrence of a hemorrhage which might be even more severe could not be excluded Thoracoscope examination might have been considered but it is doubtful if it would have served any useful purpose, and the patient's condition hardly warranted the procedure Even in several autopsied cases, no actual bleeding point could be definitely located Penicillin was administered, both intrapleurally and intramuscularly, as it was felt that every precaution against infection should be taken

## SUMMARY

The literature concerning spontaneous hemothorax and hemopneumothorax is reviewed and a case is reported in which a massive hemothorax occurred during the performance of a routine pneumothorax refill

## SUMARIO

*Caso de Hemotórax Masivo como Complicación del Neumotórax Terapéutico*

Después de repasar la literatura referente al hemotórax y el hemoneumotórax espontáneos, preséntase un caso en el cual sobrevino un hemotórax masivo durante la ejecución de una reinsuflación corriente del neumotórax

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# POLYCYTHEMIA SECONDARY TO TUBERCULOSIS OF THE SPLEEN<sup>1,2</sup>

Report of a Case and Review of the Literature

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An occasional reference is found in the earlier medical literature to a syndrome characterized by tuberculosis of the spleen and polycythemia. No adequate explanation of this relationship has ever been offered.

Tuberculosis of the spleen is arbitrarily spoken of as primary or secondary. Secondary tuberculosis of the spleen is quite common and is frequently found in generalized tuberculosis. Primary tuberculosis of the spleen (a misnomer by modern concepts of the disease, since the spleen cannot be the only or initial focus of tuberculosis) is a term reserved for those cases in which the spleen becomes involved by hematogenous spread and in which the splenic focus enlarges and caseates while the other foci either heal or become quiescent (5, 8, 12, 18, 38). Under this circumstance the spleen becomes the "primary" site for further dissemination. In attempting to classify cases of this type, it is often difficult to decide whether the other tuberculous foci are sufficiently quiescent to permit consideration of the spleen as the primary or superior site.

## *Review of Literature*

One of the most complete reviews of the subject of primary splenic tuberculosis was published by Winternitz in 1912 (44). Of 51 cases summarized, only one showed tuberculosis confined entirely to the spleen. In 40 per cent there was pulmonary tuberculosis, in 57 per cent regional lymph nodes were involved, and in 80 per cent the liver also showed tuberculosis. Sixty-six per cent of those who had tuberculosis of the lungs also had tuberculosis elsewhere. In 1924 Magnac (25) published a monograph on primary tuberculosis of the spleen and collected 19 more cases. Shands (37) was able to collect 80 cases of tuberculosis of the spleen up to 1933, and Englebreth-Holm (10) added 28 more in 1938. More cases have been reported singly since then so that there are now between 100 and 150 published cases in all. Calcification of the spleen, found on roentgenographic or post-mortem examination is considered to be tuberculous in origin. Moorman (29) collected 29 cases of splenic tuberculosis with roentgenographic evidence of calcification, but made no distinction between primary and secondary types.

Secondary splenic involvement is not rare. Klotz (22) found tuberculosis in 172 of 404 post-mortem examinations and, of these, 69 had tuberculosis of the spleen. Gohn (13) found involvement of the spleen in 55 out of 125 cases, and in a publication of the South African Institute of Medical Research (39) 51 per cent of the natives dying of pulmonary tuberculosis were reported to have had tuberculosis of the spleen as well. Hoyle and Vaizey (19) found involvement of the spleen in 31 of 110 cases of military tuberculosis.

Polycythemia was first described as a definite entity in 1892 by Vaquez (42). In this condition, too, primary and secondary types are recognized. The diagnosis of "primary" or polycythemia "vera" depends on the absence of demonstrable etiology, the presence of an elevated erythrocyte, leukocyte, and platelet count, and an increase in the blood

<sup>1</sup> From the Hematology Laboratory and the Hektoen Institute for Medical Research of the Cook County Hospital, Chicago, Illinois.

<sup>2</sup> Aided by a grant from the Wilson Laboratories, Chicago, Illinois.

volume In secondary polycythemia the elevated erythrocyte count occurs in response to increased oxygen demand In many of the reported cases it is difficult to determine whether the polycythemia is primary or secondary because of insufficient data, this being especially true in cases of the syndrome under discussion Furthermore, the division between normal and polycythemic levels must, at best, be arbitrarily set Many of the reported cases have erythrocyte counts definitely in the polycythemia range (7 to 11 million per cu mm) while others, with pulmonary or miliary tuberculosis and splenic involvement confirmed by operation or post-mortem examination, had counts but slightly over 5 0 million per cu mm Even such elevations of the count, however, are unusual since the rule is for anemia to accompany infections (34, 45), especially such severe ones as miliary tuberculosis

In the syndrome of polycythemia and tuberculosis of the spleen, the splenic involvement is not always "primary" but may be part of a generalized tuberculosis In table 1 are listed the reported cases of tuberculosis involving the spleen, both primary and secondary, where erythrocyte counts were over 5 0 million per cu mm

### *Report of Case*

At the time of her first hospital admission to the Cook County Hospital, on August 19, 1936, the patient was 23 years old The diagnosis on admission was "blood dyscrasia with splenic enlargement" Two years before admission, previous to which she had felt quite well, she became ill with "rheumatism," characterized by pain involving the ankles and knees of both feet These joints became so swollen and tender that she was unable to walk, but after resting for two weeks she felt considerably better Subsequently she had occasional pain in her feet and knees, without swelling A year later she began to have frequent sore throats, usually accompanied by fever She was advised to have a tonsillectomy, but this was indefinitely postponed because of fever Six days before admission she noted the gradual onset of pain in the left upper quadrant of the abdomen The pain was aggravated by deep inspiration, radiated to the back, and was described as a sensation of "something catching under the ribs" She had no cough, chills, or fever, but had had night sweats There was in addition, a history of frequent "boils" under the arms, bleeding from the gums following slight trauma, "sinus pains" on the right side, and weight loss During the preceding week there was a loss of appetite and almost everything caused dyspepsia

Physical examination revealed a comfortable Negro female, not acutely ill Her temperature was 99°F, the blood pressure (in mm of mercury) was 136 systolic and 78 diastolic The gums bled easily on pressure The tonsils were enlarged and red There were no palpable lymph nodes The heart was normal The spleen extended approximately 5 0 cm below the costal margin, was firm, somewhat tender, and a friction rub was heard over it The liver was not enlarged Serologic tests for syphilis (Wasserman, Kahn) were positive Diphtheroid bacilli were cultured from the throat The blood findings were as follows erythrocytes 7 36 million per cu mm, concentration of hemoglobin, 85 per cent (Sahli), total leukocytes, 9,700 per cu mm, neutrophils, 66, lymphocytes, 28, monocytes 1, and basophils 5 per 100 leukocytes On August 25, 1936 the values were erythrocytes, 7 20, concentration of hemoglobin, 110 per cent, total leukocytes, 9,000, neutrophils, 66, lymphocytes 25, monocytes 5 and eosinophils 4 per 100 cells Roentgenograms of the splenic area failed to outline the spleen or reveal any foci of calcification, while those of the chest showed bilateral increase in the markings at the hilum Examination of the bone marrow was reported as showing no evidence of leukemia

Shortly after admission the patient's temperature rose to 100°F but returned rapidly to normal and remained so for the rest of her hospital stay On September 2, 1936 she had two teeth extracted and bled from the tooth sockets for two days, in spite of packing This bleeding finally stopped spontaneously and she was discharged, feeling considerably improved

On June 8, 1937, she was again admitted to the hospital because of pain in the left upper quadrant of the abdomen and swelling of the ankles accompanied by dyspnea on exertion, present for about eight months. At first the abdominal pain was sharp in character and radiated around to the left side, but for several months it had been intermittent and accompanied by a sensation of fullness in the epigastrium. The pain was not relieved by sodium bicarbonate and at times seemed to be worse after meals. During this period her appetite had been poor and she had lost ten pounds in weight. For three days preceding admission, she had vomited following every meal. Her menstrual periods had become quite irregular.

Examination revealed dilated conjunctival vessels, gums which bled easily, carious teeth, enlarged, red, and cryptic tonsils. There was a slight depression of breath sounds over the left lung but no rales were heard. Examination of the heart revealed no abnormalities except for tachycardia. A bulge was visible in the left upper quadrant of the abdomen which, on palpation, was found to be a firm, tender spleen, the lower pole of which was 5 cm. above the left iliac crest. The liver edge was just palpable. On the lateral aspects of the legs were scattered and tender raised nodules covered with shiny atrophic skin, characteristic of erythema nodosum. There was a distinct copper hue to the skin, especially marked over the nose and malar prominences. Examination of the blood on this admission revealed the following values: erythrocytes, 6.6 million, concentration of hemoglobin, 90 per cent, total leukocytes, 17,000 per cu. mm. with 79 polys, 14 lymphocytes, 2 monocytes, 3 basophils, and 2 eosinophils per 100 leukocytes. Platelets were abundant in the blood film. There was a two plus albuminuria. The concentrations of sugar and uric acid in the blood were 68 and 7 mg. per 100 cc., respectively. Disruption of erythrocytes started at 40 per cent and was complete at 30 per cent saline. Agglutinations for typhoid, paratyphoid A and B, and melitensis were negative. A blood culture was sterile. Pelvic examination revealed nothing abnormal. A roentgenogram of the teeth showed multiple retained-root fragments and abscesses. A retrograde pyelogram showed marked rotation and distortion of the pelvis of the left kidney and defined the abdominal mass as spleen. The bone marrow at this time was reported showing proliferation of granulocytes, with no evidence of leukemia.

On April 19, 1937 the erythrocyte count was 9.15 million per cu. mm. with 126 per cent hemoglobin. The mucous membranes were cyanotic and she began complaining of frequent vomiting. She was given 0.1 Gm. of phenylhydrazine daily, and during the following week 1,000 cc. of blood were withdrawn. The vomiting persisted but the abdominal pain disappeared. A small gastric ulcer was demonstrated at this time on the posterior wall of the stomach close to and just above the incisura angularis.

On May 5, 1937 X-ray therapy to the spleen was started. On May 26, 1937 it was noted that the coppery hue of the skin was gone, the spleen was palpable only 3.0 cm. below the costal margin, her appetite was good, and she did not complain of any digestive disturbances. At the time of her discharge from the hospital, she had 6.45 million erythrocytes per cu. mm., 100 per cent concentration of hemoglobin, and 7,100 leukocytes per cu. mm. She was seen in the outpatient clinic irregularly after this and remained relatively asymptomatic until November 1938 at which time she suddenly vomited large clots of blood.

She was admitted to another hospital where she was found to have an erythrocyte count of 2.0 million per cu. mm. She received blood transfusions, improved gradually, and was discharged feeling well.

On February 9, 1939 she re-entered the hospital with a three-day history of a "cold," cough, frontal headaches, and left upper quadrant pain which was "shooting" in character. On the evening preceding her admission she again vomited blood. She did not have abdominal pain at the time and had felt fairly well since the last episode of hematemesis three months before. She did not appear seriously ill, there was tenderness over the frontal sinuses, the nasal mucous membranes were red and boggy, and the pharyngeal mucosa was granular and infected, the thyroid gland was palpable. There was no significant adenopathy. The lung fields were resonant on percussion and the breath sounds in the hilar region

were harsh. Examination of the heart was normal. The abdomen was flat except for visible fullness in the left upper quadrant due to the firm, nontender spleen which extended to the level of the umbilicus. The liver edge, firm and nontender, was palpable 3.0 cm. below the right costal arch. The deep reflexes were difficult to obtain.

During the next few days her temperature was consistently elevated (102°F being the highest) and she complained of headaches and tenderness over the frontal area. On transillumination the frontal and right maxillary sinuses were dark. The right antrum was washed and a considerable amount of pus was obtained. Her blood findings were erythrocytes, 4.85 million per cu. mm., concentration of hemoglobin, 70 per cent, total leukocytes, 18,650 per cu. mm., platelets 1,800,000. Roentgenographic examination of the stomach and esophagus failed to reveal varices or ulcers. The stools contained occult blood. The blood sugar was 57 mg. per 100 cc. and the nonprotein nitrogen, 39 mg. per 100 cc. After she had been in the hospital for about two weeks she had a sudden feeling of weakness and again vomited a great quantity of blood, the amount of which was not measured. Following this, the blood pressure dropped to 102 systolic, 60 diastolic, the abdomen remained soft, and there was no evidence of shock. The following day her erythrocyte count was 3.40 million with 12 per cent concentration of hemoglobin, and the blood pressure had risen to 120 systolic, 68 diastolic. She was given intravenous fluids for several days but continued to be nauseated and vomited occasionally. One week later she again vomited about 1,000 cc. of blood. After this the erythrocyte count was 2.65 million and concentration of hemoglobin, 38 per cent. Three days after the last bleeding episode, when her temperature was 104°F, she complained of "girdle pains" and tenderness over the lower ribs posteriorly. The spleen seemed more tender than usually. Her erythrocytes had fallen to 1.91 million per cu. mm. A week later her temperature was still elevated, she was complaining of abdominal pain and had a profuse whitish vaginal discharge in which gram positive extracellular diplococci were found. There was tenderness over the liver and spleen and in both costophrenic angles. Pelvic examination was negative. A blowing precordial systolic murmur was now noted, but blood cultures and agglutination tests were again negative. The marrow was hypercellular and revealed changes compatible with stimulation due to blood loss. Pain in the left chest, aggravated by respiration and radiating to the left shoulder appeared, the spleen became more tender, and a diagnosis of perisplenitis was entertained.

On the forty-seventh hospital day her abdomen was noted to be distended and tympanitic, there was questionable jaundice, and her temperature was still elevated. The icterus index was 10, the Van den Berg reaction was negative direct, positive indirect. In the next few days fluid began to collect in the abdomen and paracentesis yielded 1,200 cc. of cloudy yellow fluid with a specific gravity of 1.010. A smear was negative for acid-fast bacilli, the test for albumin was four plus and there were 200 leukocytes and 500 erythrocyte cells per cu. mm. On the same day she vomited a large amount of blood. A roentgenogram of the chest showed a clouding in the left base suggestive of pleural effusion. Her erythrocyte count was 2.62 million per cu. mm., hemoglobin concentration, 50 per cent, total leukocytes 8,100, per cu. mm. She was given 350 cc. of blood with no reaction and several days later 250 cc. more. The septic temperature and the vaginal discharge continued unabated. She reaccumulated peritoneal fluid, and was given 500 cc. of blood (followed by a severe chill). The next day she had an erythrocyte count of 2.34 million with 44 per cent concentration of hemoglobin. The platelet count was 410,000 and the leukocyte count, 14,150 per cu. mm. The reticulocyte count was one per cent. Three thousand cubic centimeters of yellow fluid were withdrawn from the abdomen.

Her course was steadily downhill. She continued to complain of cough and pain over the spleen. Her temperature often rose to 104°F. On two other occasions 4,000 and 3,000 cc. of fluid were removed from the abdomen. The congo red test revealed 29 per cent retention in one hour. Her last erythrocyte count was 5.21 million with 70 per cent hemoglobin. The platelet and total leukocyte counts were 230,000 and 13,400, respectively. She continued to grow weaker, became emaciated, and expired 111 days after admission.

At post-mortem examination the peritoneal cavity contained 3,000 cc. of yellowish fluid

The peritoneal surface was found to be studded with tiny yellowish-grey nodules. The periaortic and mesenteric lymph nodes were much enlarged. The liver weighed 1,200 Gm. On cut section, a biliary radicle in the right lobe was surrounded by a yellowish white area, measuring 3.0 cm. in greatest diameter. The spleen weighed 1,100 Gm. There was increased resistance to cutting and there were several well-demarcated wedge shaped infarcts. In the parenchyma, 5.0 cm. beneath the capsule, there was an 8.0 cm. circular area of caseation. The kidneys were grossly normal except for an area of caseation in the region of the lower calyx on the left. The tubes and ovaries were closely adherent and bound by multiple serosal adhesions. The heart was essentially normal. The right lung and pleural cavity were free of gross pathological changes, but the latter contained 1,000 cc. of fluid. The left pleural surface was studded with millet-sized nodules and the cavity contained 2,000 cc. of fluid. On cut surface the left upper lobe disclosed a 5.0 cm. caseous focus within its parenchyma while the left lower lobe was the site of extensive caseous pneumonia. The left hilar, tracheobronchial, and mediastinal lymph nodes were enlarged and caseous. Microscopic examination confirmed the presence of disseminated tuberculosis with caseous focal tuberculosis of the left upper lobe, tuberculosis of the hilar, mediastinal, and periaortic lymph nodes. There was a generalized tuberculous peritonitis and a tuberculoma of the left kidney. There was miliary tuberculosis of the Fallopian tubes. There was no evidence of an active peptic ulcer to explain the hematemesis. There were, however, moderately large esophageal varices but no site of previous rupture could be demonstrated. The spleen was made remarkable by the absence of the usual splenic histologic findings. Only an occasional follicle was seen. Innumerable sharply defined, widely-gaping sinusoids engorged with red blood cells were evident. The trabeculae were prominent and the stroma was densely fibrotic. In one region a diffuse organizing tuberculous perisplenitis was in evidence. There was another sharply defined area of tuberculous necrosis in the parenchyma. The areas of infarction were necrotic and surrounded by leukocytes and a zone of hyperemia.

It was felt that this case represented a childhood type of primary pulmonary tuberculosis with secondary miliary dissemination and extensive splenic involvement.

#### DISCUSSION

The triad of cyanosis, polycythemia, and splenomegaly was suggested by Rosengart (35) as being diagnostic of primary tuberculosis of the spleen. It is now realized however, that this triad is commonplace in polycythemia rubra vera. Abdominal pain, a palpable spleen, or both, characterized tuberculosis of the spleen in 70 per cent of Winternitz's (44) cases. Weakness and loss of weight were also usually present. Winternitz, however, pointed out that these cases may have an onset not unlike an acute infection with collapse, fever, chills, backache, and acute clinical course. The blood picture is inconstant. Blood counts were done in 26 of his 51 cases, and of these 9 were normal, 11 had anemia, and 6 had polycythemia. We were able to find 29 additional cases having erythrocyte counts over 5,000,000 per cu. mm. Fifteen of these were considered to have "primary" tuberculosis of the spleen. Ten of these, plus our own case, can be considered as having significant polycythemia. Head's (14) case of polycythemia with splenomegaly cannot be accepted as secondary to splenic tuberculosis since the only evidence offered is a positive Mantoux test. The combination of tuberculosis, polycythemia, and splenomegaly may be misleading. Leon-Kindberg (21) presented a case with an erythrocyte count of 8.5 million per cu. mm., fibrous pulmonary tuberculosis and a splenomegaly, but post-mortem examination failed to show any evidence of tuberculosis in the spleen.

Cases 8, 16, and 25 can be accepted on fairly good evidence. Zadek's (46) case (No. 25) had a tuberculous iridocyclitis, pulmonary tuberculosis, and a splenomegaly. The patient's first Mantoux test was negative. Subsequent counts were lower, the Mantoux test became positive, and with clinical improvement the spleen became smaller. Mauriquand's

TABLE 1

*Summary of Reported Cases of Tuberculosis Involving the Spleen (both Primary and Secondary) in which Total Erythrocyte Counts of over Five Million per cu mm Were Recorded*

	AGE	SEX	RBC	HGB	WBC	SPLEEN	SPLEEN TCT ONLY	EXTENT OF SPLENIC INVOLVEMENT	PRESENCE OF MILIARY TUBERCULOSIS
1 Barlaro (1)			6.5				no	Not stated	Probable Lesions of kidney, bladder and spleen
2. Bayer (2)	53	M	6.0	40%	7,500	1,750 G	yes	Myriads of small conglomerate tubercles	Unknown Patient recovered after splenectomy Lungs and liver not grossly involved
3 Brown et al (3)	54	M	5.2	14*	1,500	2,700	no	Diffuse small areas of tuberculous necrosis	Lungs negative but tuberculosis demonstrated in spleen, liver nodes liver hilum and one para tracheal node
4. Brunard (4)	7	M	6.0	50%	8,000		no	Not stated	Probable Lungs involved, cervical adenitis, ascites
5 Cominotti (5)	33	F	7.5	80%	6,000	2,250	yes	"Much scarred"	Probable "Carries of spino" and one small tuberculous nodule in liver
6 Coyon (7)	56	M	7.9	95%	42,000		no	Spleen bugs with large and small tubercles Microscopic diffuse caseation	No Spleen apparently primary site at time of autopsy No miliary tubercles
7 Douglas et Eisenbrey (9)	39	M	8.8	120%	23,000	1,350	yes	Diffuse small areas of necrosis There was one large area of infarction showing complete necrosis	Yes Lungs liver splenic bed, diaphragm
8 Forrester (probable) (11)		F	7.2	103%	21,000		no	Calcification noted in spleen on roentgenogram	Unknown Patient alive at time of report
9 Heyman (15)	3		5.58	72%			no	Two identical sized spleens and five smaller ones involved in caseous tuberculosis	Yes Lungs mediastinum, and colon
	3		5.68	80%			no	"Numerous tubercles in spleen"	Yes Lungs, meninges, liver, spleen et cetera
	child		6.6	84%			no	"Extensive tuberculosis of spleen up to pea sized tubercles"	Yes Lungs, mediastinum lymph nodes, meninges, brain, et cetera
	7†		5.2	92%			no	Not stated—"miliary tuberculosis of spleen"	Yes
	13†		6.2	67%			no	Not stated—"miliary tuberculosis of spleen"	Yes



TABLE 1—*Concluded*

	AGE	SEX	RBC	HGB	WBC	SPLEEN	SPLENECTOMY	EXTENT OF SPLENIC INVOLVEMENT	PRESENCE OF MILIARY TUBERCULOSIS
10 Hickling (16)			5 1	100%	5,300		yes	Splenic tissue almost entirely replaced by tissue showing microscopic features to tuberculosis with typical focal arrangement but without caseation	Yes Roentgenographic evidence in lungs
11 Jedwabnik (20)	49	M	20 mil?	170%	5 000		no	Spleen enlarged Numerous miliary to pea sized partly confluent irregularly outlined grey white foci	Yes
12 Lambert et Bottin (23)	53	F	5 2	80%	1 900		yes	Diffuse	Unknown Patient recovered after splenectomy
13 Lederer (24)	49	M	9 7	140%	6 600		no	Capsule studded with pin head to lentil sized foci	Yes Liver lungs, kidney
14 Margolis (26)	57	M	7 05	110%	5 800		no	Spleen very large—changes apparently diffuse	Not stated
15 Matzdorff (27)	59	M	5 6	105%	15 000		no	Diffuse	Yes Both lungs
16 Mauriquand (probable) (28)	11†		9 2	95%	5 000		no	Not stated Spleen enlarged	Probable
17 Moutard Martin et Lefas (30)	49	F	8 20		1 750		no	"Many caseous nodules "	Probable Calcified nodules in lungs, liver and mesenteric nodes
18 Pether (31)			5 64	80%	7 500		no	Spleen studded with nodules having central caseation	Yes Apices of lungs, brain, stem, kidneys
19 Rendu et Vidal (32)	40	M	6 20		6 000	3 780	no	Conglomerate tubercles and sclerosis	Yes Lungs liver kidneys, pancreas
20 Rennen (33)	67	M	8 60	130%	13 400	1 900	no	Numerous grey and white caseating nodules pin head to pea sized	Yes Lungs liver kidney and bone marrow
21 Sachs (36)	58	M	11 00	150%	25 000	700	no	Diffuse miliary tubercles	Yes Hilar nodes
22 Strehl (40)	64	F	6 5	120%	12 000	1 000	yes	Numerous large and small foci with partial central caseation One apple-sized wedge-shaped focus	No TB in other organs
23 Szezechlik (41)	39	F	7 8	76%	5 900	1 950	yes	Not stated	Not autopsied Pulmonary tuberculosis showed on roentgenograms
24 Weil (43)	56	F	6 55	90%	48 000	1 350	no	Tubercles visible macroscopically	Not stated
25 Zudek (probable) (46)	31	F	6 62	110%	8 200		no	Unknown	Probable

\* Gm

† Non Is

(28) case (No 16) was an 11-month-old infant with ascites, purulent pleural effusions, purulent lymph node abscesses, splenomegaly, and a positive Mantoux test. Guinea pig inoculation of material from the pleural effusion and the abscess revealed tuberculosis. Forsell's (11) case (No 8) had a polycythemia and roentgenographic evidence of calcium deposits in the spleen.

Polycythemia with pulmonary tuberculosis is rare. Holzberg (17) in 1929 reported the case of a 21-year-old male who had bilateral active pulmonary tuberculosis with sputum positive for tubercle bacilli and characteristic roentgenographic findings. In spite of repeated massive pulmonary hemorrhages, he maintained an erythrocyte count around 5.0 million with a hemoglobin of 90 to 105 per cent. Hayman (15) reported his analysis of tuberculosis in children with and without polycythemia and attempted to show that the polycythemia was not related to the splenic involvement, but rather to miliary tuberculous involvement of the lungs. If this were the case, however, polycythemia should be seen much more often than is the case in tuberculosis. There has, as yet, been no satisfactory explanation offered for the coexistence of these two conditions.

Many feel that the diagnosis of primary tuberculosis of the spleen is an indication for splenectomy. In Winternitz's (44) series of 51 patients, 17 had splenectomy performed and 59 per cent of these recovered. Of the 29 cases in which polycythemia and tuberculosis of the spleen coexisted, 7 had splenectomies. Of these, 4 patients died. In one (9), the erythrocyte count was still 8.8 million per cu. mm. on the ninth postoperative day, shortly before death. In another (40), the count after splenectomy went to 7.2 million with hemoglobin of 115 per cent, and 27,000 leukocytes per cu. mm. Of the 3 patients who recovered, there was no note of the blood count following surgery in one, but there was roentgenographic evidence that the miliary tuberculosis had cleared five years later. In the second, the initial count of 5.2 million went down after surgery, but gradually returned to the same count after four and one-half months. In the case of Bayer (2), the postoperative erythrocyte count was 6.0 million, but one month after surgery the count was 1.32 million per cu. mm. From these results it is difficult to evaluate the effect that splenectomy has on the polycythemia, the results being inconsistent and the series too small.

#### SUMMARY

1. A review of the literature disclosed 35 cases of tuberculosis of the spleen and polycythemia, to which another case is added.

2. Splenectomy is the treatment of choice if the diagnosis of primary tuberculosis of the spleen can be made. What effect this procedure will have on the coexisting polycythemia is problematical since the frequency of successful splenectomies in the past is too small for evaluation.

#### SUMARIO

##### *Politemia Secundaria a Tuberculosis Esplénica. Comunicación de un Caso y Repaso de la Literatura*

1. Un repaso de la literatura reveló 35 casos de tuberculosis del bazo y politemia, a los cuales se agrega otro caso.

2. La esplenectomía es el tratamiento de elección, si puede hacerse el diagnóstico de tuberculosis primaria del bazo. El efecto de este procedimiento sobre la politemia coexistente resulta problemático por ser insuficiente para justipreciación el número de esplenectomías acompañadas de éxito en el pasado.

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## EDITORIAL

### Immunological Aspects of BCG Vaccination

There have been endless controversies concerning the dangers and effectiveness of immunization with the BCG vaccine. Surprisingly enough, however, little has been said or written concerning the immunological basis and the technical problems involved in the preparation of the vaccine or the measurement of its protective efficacy. Opponents as well as proponents of BCG vaccination seem to accept implicitly that the technical procedures advocated by Calmette and his associates for growing the microorganism, preparing suspensions of it, and assaying the development of immunity, are fundamentally adequate and need not be modified except in detail. This is a questionable assumption and there is much reason to suspect that many of the controversies elicited by BCG vaccination cannot be settled until a number of bacteriological and immunological problems have been solved. Indeed, it is not unlikely that many of the failures of vaccination can be traced to the utilization of defective vaccines and to the lack of techniques for differentiating between allergy and protective immunity.

The BCG vaccine is a suspension of living tubercle bacilli obtained from cultures of a strain so attenuated as to be incapable of causing progressive disease in experimental animals. It is almost certain that the immunity produced by the vaccine is the outcome of a limited but definite multiplication of the attenuated bacilli in the body of the animal undergoing immunization, chiefly in the regional lymph nodes. The degree of immunization probably reflects in a certain measure the extent of this multiplication. It is very likely, on the other hand, that the degree of multiplication depends in turn upon at least four independent factors: (a) the number of living microorganisms injected, (b) their physiological state, (c) their level of attenuation (or virulence), (d) the susceptibility of the immunized individual.

As far as can be judged from published experimental data and from present practice, these factors are not yet sufficiently understood to permit critical and quantitative assessment of the properties of the vaccine.

It is generally recognized that the numbers of viable bacilli in the BCG vaccines prepared by standard methods and kept in fluid medium decrease rapidly, even at ice box temperatures, considerable mortality of the bacilli also occurs at the time of desiccation when attempts are made to preserve the bacilli in the dried state. Although no adequate quantitative bacterial counts have been published, it is certain that the numbers of viable organisms injected as an immunizing dose under the conditions of present day practice vary many thousandfold, depending upon the origin of the vaccine, the time elapsed since its preparation, and the conditions under which it has been preserved. As measured by direct microscopic count or by dry weight of bacillary bodies, the vaccines currently distributed in this country and abroad contain from 1 to 5 billion bacterial cells per cc. of fluid. Viability tests reveal, however, that only a fraction of a per cent

of these cells, at times less than 0.01 per cent, are viable at the time of injection. In view of this fact, the general practice of giving directions in terms of cc or mg of vaccine is entirely meaningless and perhaps dangerously misleading since it tells nothing of the number of living bacilli per volume or unit weight.

The ability of all bacterial agents to multiply in the animal body, and the tubercle bacillus is no exception, depends not only upon the size of the viable infective dose but also upon the physiological state of the bacterial cells at the time of injection. The conventional techniques used in the cultivation and distribution of the BCG vaccine expose the bacilli to such a variety of chemical and physical trauma that any vaccine preparation consists of an unpredictable mixture of cells possessing all degrees of physiological age and activity. It is therefore imperative that techniques be worked out to obtain bacterial populations of a reasonable degree of homogeneity in order to control their ability to multiply *in vivo*.

It is obvious that, in addition to its physiological state, the intrinsic virulence of a culture is a determining factor of the extent to which it multiplies in susceptible animals. At least three general levels of intrinsic virulence have been recognized among mammalian tubercle bacilli. They are represented by

- (a) the classical virulent strains capable of causing progressive disease,
- (b) the truly avirulent variants (illustrated by the various Ra cultures isolated at the Trudeau laboratory) which appear completely incapable of multiplying *in vivo*, and
- (c) the "attenuated" strains which multiply to a certain extent *in vivo* but fail to cause progressive disease under normal conditions (such are the BCG strains and the culture R1RV isolated at the Trudeau laboratory).

As far as is known, all the strains of BCG presently in use are derived from the attenuated culture first obtained by Calmette and Guérin. Although there is as yet no incontroverted evidence that this culture has ever recovered full virulence, there is no doubt that it has undergone considerable variations in the course of its long career. And indeed, it would be very surprising if it had not. K. A. Jensen, for example, has pointed out that the strains available in Scandinavia at the end of World War II varied appreciably with reference to the severity of the skin lesions which they could elicit in normal guinea pigs. Similarly, it has been observed in our laboratory that three strains of BCG obtained from American collections differ significantly in their ability to produce pulmonary lesions in mice following intravenous injection. Here again, studies of the comparative virulence (or attenuation) of different strains will have quantitative meaning only when the inoculation dose is defined in terms more significant than the designation of the volume or weight of culture used.

It must be remembered also that any statement concerning the virulence of a culture should be qualified by specifying not only the species and the breed, but also the physiological state of the animal used for the test. Thus, it has been shown at the Saranac laboratory that the strain R1RV (in many respects difficult to differentiate from BCG) causes severe disease in the silvotic guinea pig but not in normal animals. It has also been found in our laboratory that one of the BCG strains commonly used for immunization can cause severe pulmonary

disease (and sometimes death) when injected in sufficient amounts into mice maintained on deficient diets. Presumably in most studies the physiologic state of the animals has not been altered in such a fashion. It is possible, however, that some of the conflicting reports concerning the virulence of BCG for guinea pigs might reflect the presence of differences in the physiologic state of the animals used by the various investigators.

Any immunization procedure must be standardized in terms of the specific goal for which it is employed. It is highly desirable, therefore, that BCG preparations be standardized in terms of their ability to induce immunity against tuberculous infection. Surprisingly enough, there is as yet no well defined technique for such an assay.

Most tests aimed at evaluating the immunizing efficacy of BCG have been carried out by injecting into guinea pigs or cattle amounts of vaccine far greater than those used in human vaccination. In some cases the amounts were so great (of the order of 10 mg. of bacillary bodies per Kg. of body weight) that a definite degree of immunity could have been achieved with the same weight of bacilli killed by heat. Needless to say, immunization tests carried out under such conditions do not reflect the immunizing efficacy of the vaccine as used for immunization of humans.

Of extreme importance also is the technique employed in the challenge infection used to assay the resistance of the immunized animal. When tubercle bacilli are injected intramuscularly or subcutaneously into immunized guinea pigs, they elicit the complex allergic reaction familiarly known as the Koch phenomenon. One of the results of the Koch phenomenon is that a large percentage of the bacilli are ejected from the tissues as soon as the lesion elicited by the allergic reaction begins to ulcerate. As this reaction does not take place in normal animals, it follows that the immunized guinea pig is subjected in fact to an infective dose of bacilli smaller than that which invades the tissues of the non-immunized controls.

For lack of quantitative information, it is not possible to evaluate the effect of this discharge or walling off of bacilli at the site of the ulcer on the greater resistance to artificial infection exhibited by vaccinated guinea pigs. It appears certain, however, that the importance of this effect is not small, as any decrease in the size of the infective dose markedly increases the survival time of the animals. Thus, in certain cases, the apparent immunity of guinea pigs following BCG vaccination might be nothing but a sort of immunological artifact resulting from the loss of a significant fraction of the inoculum.

It is possible that the shedding or walling off by the vaccinated guinea pigs of some of the bacilli injected intramuscularly or subcutaneously has its counterpart in human infection. But, even then, it is probable that many of the bacilli are distributed throughout the human tissues instead of being discharged outside the body. Thus, the Koch phenomenon, which probably results in some protection of the vaccinated guinea pigs against artificial infection, may fail to have a corresponding protective effect under the usual conditions of the human disease. Fortunately, there are many facts which suggest the existence of an

antituberculous immunity completely independent in its mechanism from tuberculin allergy. Much additional work is therefore required toward the formulation of techniques for evaluating the effectiveness of BCG as an immunizing agent under conditions that would reflect the processes at work in the human body.

In the final analysis the usefulness of BCG immunization must be measured by its ability to protect human beings and cattle against tuberculous infection. Field trials in cattle have been so unconvincing that the technique has never achieved widespread application in veterinary medicine. There are, however, a few studies on record which appear to prove that, in selected situations and when the immunization tests are carried out with sufficient care, it is possible to achieve with BCG vaccination a significant degree of immunity in human populations. There are also, on the other hand, many records of failure. It has been argued that these failures were due to faulty immunization procedures but there is no way to prove or disprove this contention because there is no method, short of infection, to measure protective immunity.

The development of a positive tuberculin test is universally used as a criterion that the vaccine has "taken" but, unfortunately, as already pointed out, the relation of tuberculin allergy to immunity is one of the most obscure aspects of the pathogenesis of tuberculosis. It is possible to render animals tuberculin positive by injecting dead tubercle bacilli into them without increasing thereby their resistance to infection. It is well possible that under certain conditions injection of BCG may also bring about a state of allergy without inducing immunity. So important is the necessity to differentiate between allergy and immunity that it may be useful to illustrate the difference by examples taken from two other bacterial infections.

The use by Pasteur of living attenuated cultures for immunization against anthrax (the first forerunner of BCG immunization) resulted in spectacular protection of animals provided the challenge infective dose was given within a fairly short period of time after vaccination. Pasteur himself, however, soon recognized that the immunity was only transient and he advised that the vaccination be repeated every year, preferably just before the beginning of the anthrax season. Nevertheless, it is now known that long after vaccination has lost its protective effect against infection there are still present in the vaccinated animal antibodies, some of which are capable of giving rise to allergic reactions, which bear no relation whatever to immunity. To look for these anthrax antibodies would give no information as to the resistance of the animal to anthrax infection.

The extensive knowledge of the immunochemical reactions involved in streptococcal diseases affords also a striking example of dissociation between immunity and allergy. Infections caused by human streptococci of group A bring about a state of tuberculin-like allergy to the streptococcal "nucleoprotein" fraction. It has been demonstrated beyond doubt that, far from resulting in any increased resistance to streptococcus disease, this allergy may be the cause of severe pathologic lesions. On the other hand, a highly effective and type-specific resistance



to infection is elicited by an antibody specifically directed against an entirely different streptococcal protein, the so-called M substance. It has been thoroughly established that the state of allergy to the "nucleoprotein" and the immune resistance due to the M antibody are completely independent one from the other. Following natural infection or immunization, both allergy and resistance may coexist or only one may be present, depending upon certain immunological conditions that need not be discussed here. Thus, a test devised to measure streptococcal allergy does not measure resistance to streptococcus infection and, by analogy, the tuberculin test does not necessarily reflect immunity to tuberculosis.

It must not be forgotten, moreover, that the response of an individual to an immunizing procedure is greatly affected by his physiological state. It is even conceivable that many of the classes of human beings who are most dangerously exposed to tuberculosis (*for example those living under conditions of great economic stress, with inadequate food supplies*) may be those least capable of responding satisfactorily to immunization procedures. For all these reasons, it is urgent that techniques be developed for the measurement of true immunity (not tuberculin allergy) in order that the BCG immunization programs can be intelligently controlled.

Unfortunately, we are still in complete ignorance of the immunological mechanisms, humoral or cellular, which bring about immunity to tuberculosis. It is not yet possible, therefore, to devise any laboratory test that would control the effectiveness of BCG vaccination. Nevertheless, BCG is the only immunizing agent for which there is enough experience to warrant administration to human beings, and the urgency of the practical problems of tuberculosis may compel its use even though so much is ignored of its immunological properties.

The advisability of undertaking a BCG immunization program in any given community has to be decided on the basis of many clinical, epidemiological, and social factors which do not come within the province of the present discussion. But what we have tried to emphasize is that BCG immunization, like any other public health measure, must satisfy a number of minimal requirements of dependability, predictability, and evaluation of efficacy. It is because these requirements were ignored that most of the vaccines and sera introduced into medical practice in the past have now been completely discredited. It is to be feared that the same fate will happen to BCG, unless steps are taken soon to learn to control the factors which determine the efficacy of immunological procedures, namely the effective size of the immunizing dose, the antigenic potency of the vaccine, and the response of the immunized individual in terms of protective immunity. The analysis of these factors and the development of techniques by which they can be quantitatively evaluated come within the range of the classical approach to bacteriological and immunological problems and would seem to be the responsibility of those who advocate the widespread use of BCG as an immunizing agent.

Reif J. Duno-

## BOOKS

GERHARD HERTZBERG *The Achievements of BCG Vaccination* Pp 270 I Johan Grundt Tanum Forlag, Oslo, Norway, 1948

In spite of the fact that BCG is being widely used throughout the world at the present time in an attempt to immunize against tuberculosis, the subject of its use is still highly controversial.

It is generally agreed that a great deal is still to be learned concerning the degree of immunity the vaccination confers, the stabilization of its potency, the optimum method of use, the optimum dosage, the duration of the immunity conferred, and adequate means of testing the duration of immunity.

Studies which will add to our information on any of these or related subjects concerning BCG are being awaited with the greatest interest.

In *Achievements of BCG Vaccination* by Gerhardt Hertzberg, a great mass of valuable information is collected and illustrated by material from the Tuberculosis Department of the Oslo Public Health Service.

Investigations on the influence of sex, age, and dose, as well as studies on the virulence of BCG and on the size of the local reaction, are presented with statistical analyses. Other studies presented include those on the size of the local reaction and its relation to the development of tuberculin sensitivity, the duration of the tuberculin allergy following vaccination, the possibility of ill effects following vaccination, and the results of various investigations throughout the world on tuberculosis morbidity and mortality following vaccination with BCG, with special reference to the results obtained by the Tuberculosis Department of the Oslo Public Health Service.

The difficulties of conducting a BCG program on a public health basis, where vaccination and follow-up are entirely on a voluntary basis are clearly presented. As an example, it was hoped that all BCG-vaccinated persons could be tuberculin tested and examined roentgenographically one year after vaccination but, in spite of all attempts to return them to the clinics, there remained an extremely high percentage of absentees. With our present indefinite knowledge of BCG activity, the tuberculin test at the end of the year seems most necessary for, if the test has reverted to negative, revaccination is advised.

A section of the book is devoted to information obtained on the duration of tuberculin sensitivity following the BCG inoculation by various methods employed. The results of these studies are of great interest, for they show that the duration of the vaccination allergy is not a constant factor but is influenced by the degree of tuberculin sensitivity following BCG vaccination. Regardless of method of vaccination, the greater the tuberculin sensitivity following vaccination, the longer the duration of tuberculin allergy.

A further finding was that the duration of tuberculin allergy was longer following intracutaneous inoculation than when the multiple puncture method of Rosenthal was used.

Among the interesting sections in the book is one dealing with the virulence

of the vaccine It is pointed out that "Calmette's original claim that he had succeeded in converting the BCG strains into a virus fixe is no longer upheld by authorities on BCG" Evidence is presented showing that the virulence of the vaccine may decline to such a degree that it provokes no tuberculin reaction On the other hand, Jensen is quoted as stating that "if the strain becomes too virulent, abscesses develop with alarming effect" According to Jensen, the most sensitive criteria known for determining the virulence of a given vaccine are the size of the local reaction, the frequency of development of tuberculin sensitivity after vaccination, and the degree of tuberculin sensitivity on re-examination two months after vaccination

However, in spite of the fact that at times a certain increase in virulence of the vaccine occurs it must be added that there is no evidence that it has at any time created any greater hazard than the production of local lesion abscesses As a matter of fact, the more frequent difficulty has been a diminution in the virulence of the vaccine This problem, which has been discussed in the United States, is of practical importance The vaccine, as used, is an emulsion of BCG in suspension in which there may be great variations per unit of volume in the total number and in the relative numbers of living, damaged, and dead BCG organisms It is difficult, therefore, to have full dependence on a vaccine suspension where the potency is much higher on the second or third days than on the eighth or ninth days after preparation

The material presented seems to give no support for the assumptions that BCG vaccination is harmful in the pre-allergic stage or that natural tuberculosis infection in the incubation period of BCG vaccination is dangerous However, it is emphasized that, as far as can be ascertained, BCG vaccination does not afford any protection against tuberculosis when natural infection occurs before complete vaccination allergy has been achieved

In any publication of the subject of BCG the greatest interest lies in the section dealing with the efficacy of the vaccine in the prophylaxis against tuberculosis

Before presenting the results of their own investigations, a summary is made of certain other studies reported from various countries These are the same studies which have so often been presented and criticized in discussions on the efficacy of BCG

In some studies the value of the vaccine is claimed on basis of a reduction in tuberculosis morbidity in the vaccinated cases But since the BCG inoculation is the primary tuberculosis focus, one should not expect the benign exudative pulmonary process in exposed vaccinated cases while expecting a certain number among the controls

Studies are presented entirely lacking in controls Among these is the study of Wallgren in Gothenberg "where practically no control material was available" In this city where, with very few exceptions, all infants exposed to tuberculosis were vaccinated with BCG, the fall in tuberculosis mortality dropped in a six-year period from 400 to 30 per 100,000 for infants, whereas the general tubercu-

losis mortality dropped from 200 to only 100 per 100,000 in the same period of time

These figures appear of great significance by themselves but when a comparison is made with the figures from New York City, where BCG was not used, the importance becomes less pronounced

In New York City with a population that includes over 600,000 Negroes, the tuberculosis mortality in children under the age of 15 years has dropped 94% since 1915. In that year the tuberculosis mortality was 81 per 100,000, whereas in 1947 it was only 5 per 100,000, a significant reduction

The carefully controlled studies on BCG in New York City, where very little difference in the tuberculosis mortality was found between vaccinated and control cases, are criticized on the ground that the children were in many instances permitted to return to a tuberculous environment immediately after vaccination

On the other hand, the favorable studies of Aronson are praised although his cases were not selected by alternation, as had been carried out in New York City, and in spite of the fact that no separation was attempted or carried out

Among the studies presented in the book is one that deserves special attention. This is a report by Hyge of 200 girls between the ages of 12 and 18 years who were exposed to a tuberculous teacher in a school in Denmark. One hundred and six of the girls had received BCG whereas 94 were tuberculin-negative but had not been vaccinated

Of the 106 girls who were vaccinated with BCG and who were exposed, 2 developed pulmonary tuberculosis within three years requiring pneumothorax treatment. On the other hand, of the 94 girls not vaccinated, 79 became tuberculin-sensitive, among whom 41 developed pulmonary tuberculosis (37 with tubercle bacilli found on gastric lavage). After three years, one had died of tuberculosis and 5 were undergoing pneumothorax.

This report would seem to give support to the impression that the pulmonary infiltration of primary tuberculosis is much more likely to become progressive and advance to caseation in the adolescent than in the young child. If this is true, then vaccination with BCG, which places the primary focus at the point of inoculation, would be most valuable since it is extrapulmonary.

Of greatest interest to the reader is the report of the studies conducted in Oslo by the Public Health Service under the supervision of the author himself, Doctor Hertzberg. What scientific standards of investigation were laid down and what efforts were made to obtain adequate controls, controls which could be truly comparable to the individual vaccinated?

On page 30 one comes across an amazing statement, "The main qualifications for inclusion in the control material is the evidence (in our records) of recent infection with tuberculosis in persons who had earlier been tuberculin negative."

In other words, every individual vaccinated with BCG gave no evidence of having been infected with tubercle bacilli, while every control was already infected with tubercle bacilli. "No one is vaccinated with BCG unless he is Mantoux-negative to 10 mg. of Old Tuberculin."

Such experimental methods immediately destroy any value to be obtained from a study of tuberculous mortality statistics

Needless to say the tuberculosis mortality in the control groups is very much greater than that of the vaccinated group, a ratio of 45 to one

It is indeed unfortunate that in this volume prepared under the supervision of statisticians one can gain no further information as to the efficacy of BCG

However, there is a great deal to be found concerning the side effects of BCG, such as local reaction and its relation to duration of tuberculin sensitivity, discussions concerning the potency and virulence of the vaccine, and studies on superinfection after loss of vaccination allergy An excellent bibliography is also included

MILTON I LEVINE  
NEW YORK CITY

CARL MALMBERG *140 Million Patients* Pp xii + 242 Reynal & Hitchcock, New York, 1947 Paper Price \$2.75

This book emphasizes some defects in American medicine today Its subtitle, *The Revealing Facts Behind Health and Medical Care in America*, is misleading, and might better read *Some Revealing Facts Behind Health and Medical Care in America*, for the author deals in considerable detail with many medical defects, whereas he passes over the excellencies of American medicine in glittering generalities However, his data are worthy of consideration, for he brings out many points all too often ignored by medical men

The author, we are told, has been a public relations advisor, information specialist for the United States Public Health Service, and Chief Investigator for the United States Senate Subcommittee on Health and Education

In his first chapter, *Health Inventory—U S A*, he attacks the often heard idea that the United States is the healthiest country in the world by quoting what would seem to be reasonably valid statistics compiled by the Department of Commerce, Bureau of the Census He shows that in 1938, considered the last normal pre-war year, 7 countries showed a lower *crude* infant mortality rate in those under one year old per thousand live births, Iceland showing the lowest As to maternal mortality per thousand live births, 21 countries showed lower crude rates, Japan having the lowest What *corrected* rates would show, we do not know While the tuberculosis death rate between 1920 and 1936 decreased in the United States 51.2 per cent, five countries showed an even greater percentage decrease, the Netherlands leading with a decrease of 66.0 per cent

In *The Cost of Sickness*, expensive proprietary drugs as well as patent medicines are properly scored Rebates to physicians on high charges for the rental of oxygen equipment to patients and on prescriptions for eyeglasses are justly condemned The economic waste of competing costly equipment owned by individuals is discussed Blatant quackery and voodooism are mentioned

*How Good is American Medical Care?* lists many examples of medical incompetence and inefficiency, both individual and institutional The inequality of dis-

tribution of medical care is also discussed. Unnecessary operations are properly castigated. Even the free clinics of Washington, D. C. are a target for the author. A quotation said to be verbatim from certain testimony before the Senate Committee on Education and Labor, if correct and not torn from its context so as to distort its meaning, seems worth quoting in part:

*Senator Pepper* "Do you think the American people have all been well?"

*Dr. S.* "Yes, I know that they have."

State service for crippled children is deservedly praised.

Mr. Malmberg favors President Truman's sixfold program, which includes

- 1 federal financial aid to build hospitals, health centers, et cetera,
- 2 federal aid in expanding public health and maternal and child health services,
- 3 federal aid to train doctors and health workers and for medical research,
- 4 incorporation of health insurance in our social security system,
- 5 cash insurance protection against loss of earnings from sickness or disability.

Mr. Malmberg, admitting that item 4 is the most controversial one, believes that item 1 depends on it, for it would be of little use to build hospitals that people could not afford to use.

*Voluntary Plans, Too Little and Too Late* attacks the ultraconservatism of the A. M. A., which seems at times to have followed, rather than led, the movement for better medical service to the underprivileged and isolated. Often Negroes are excluded from voluntary insurance plans.

The final chapter, *140 Million Patients Can't Be Wrong*, expresses the idea that the people of the United States, i. e., the potential patients, will determine the type of the medical practice of the future. The chapter title is a half-truth, for a large number of the 140 million patients consume an incredible amount of useless or worse patent medicine, as Mr. Malmberg admits. We wonder if the volume of work, expressed in financial terms or in the number of patients, of the best clinics in the country can equal that of the most notorious patent medicine businesses. The latter gives evidence that a vast number of the 140 million patients *can* be wrong.

The book is an able argument for socialized medicine, but ignores the arguments against it, such as the destruction of the will to get well, et cetera. Space forbids the presentation of the other side. With about 180,000 doctors in the United States and with human nature as fallible as it is, there must be numerous cases of incompetence or neglect under any system of practice, individual or socialized. Very few physicians want completely socialized medicine. None want to assume individual care of all the insane. Most of us want a great increase in both the quality and quantity of the care of mental patients by the state and of many other chronic cripples unable to care for themselves. However, whatever our views on the degree of socialization of medicine that is desirable, we would be worse than foolish to deny the existence of defects in our present day methods. We must face them and constantly strive to eradicate them and build constructively for a better future.

If Mr Malmberg proves to be a Socratic gadfly that stings us into a realization of our deficiencies, he will perform a useful task. The combined sincere thought of conscientious, balanced, enlightened people, in and out of the medical profession, may serve as a Socratic midwife to determine which of the author's ideas are true births and which are expulsions of wind. We do not think that any enlightened person can condemn the book as all wind. Rather we believe that it contains much truth, some error, and *it certainly fails to present the essential weaknesses in socialized medicine*. It is a good antidote for ultraconservatism in medicine, but might well be published in a single volume along with as frank a discussion of the evils of socialized medicine as the author gives of the evils of a system based on rugged individualism or a too slavish adherence to tradition.

FREDERICK R. TAYLOR

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# AMERICAN TRUDEAU SOCIETY

## Medical Section of the National Tuberculosis Association

### STATEMENT ON BCG

(Revised statement submitted to the ATS Committee on Medical Research and Therapy in Detroit, April 30, 1949, by Dr E P K Fenger, Oak Terrace, Minnesota, chairman of the Subcommittee on Immunology, and subsequently submitted to the ATS Council at its meeting in Detroit on May 1, 1949, through Dr H McLeod Riggins, chairman of the Committee on Medical Research and Therapy. The statement as revised was adopted by the Council.)

The members of the Society and other physicians in the United States have been interested for many years in the active immunization against tuberculosis with BCG. The expansion of public health activities in the field of tuberculosis control by official and voluntary agencies and the acquisition of new knowledge concerning immunity in tuberculosis have prompted the American Trudeau Society to make the following observations and recommendations:

- I BCG vaccine prepared under acceptable conditions, and administered by approved techniques to persons negative to tuberculin, can be considered harmless.
- II The degree of protection recorded following vaccination is by no means complete, nor is the duration of induced relative immunity permanent or predictable. The need for further basic research on the problem of artificial immunization against tuberculosis is recognized and is to be emphasized. Studies should be directed toward:
  - (a) improvement of the immunizing agent,
  - (b) development of criteria for vaccination and revaccination,
  - (c) more accurate determination of which groups in the general population should be vaccinated, several well controlled studies are underway at the present time,
  - (d) promotion of carefully controlled investigative programs, which, as a rule, will be carried out best under the auspices of official agencies such as the Public Health Service, state and municipal health departments, and other especially qualified groups,
  - (e) devising of adequate record systems for management of statistical problems involved in recording and following large numbers of vaccinated people.
- III On the basis of studies reported in the literature, an appreciable reduction in the incidence of clinical tuberculosis may be anticipated when certain groups of people who are likely to develop tuberculosis because of unusual exposure, inferior resistance, or both, are vaccinated.
  - (a) In the light of present knowledge, vaccination of the following more vulnerable groups is recommended, provided they do not react to adequate tuberculin tests:
    - 1 doctors, medical students, and nurses who are exposed to tuberculosis,
    - 2 all hospital and laboratory personnel whose work exposes them to contact with the bacillus of tuberculosis,
    - 3 individuals who are unavoidably exposed to infectious tuberculosis in the home,



- 4 patients and employees in mental hospitals, prisons, and other custodial institutions in whom the incidence of tuberculosis is known to be high,
  - 5 children and certain adults considered to have inferior resistance and living in communities in which the tuberculosis mortality rate is unusually high
- IV It is recommended that efforts be continued to perfect and to meet in practice suitable standards for the production of BCG vaccine and that, when practicable, commercial firms be licensed under the National Institutes of Health to produce this vaccine
- V The Society believes that, since BCG vaccination affords only incomplete rather than absolute protection, the most effective methods of controlling tuberculosis in the general population are
- (a) further improvement of living conditions and the general health,
  - (b) reduction of tuberculous infection, which can be accomplished by modern public health methods and the unremitting search among presumably healthy individuals for patients with infectious tuberculosis,
  - (c) prompt and adequate medical and surgical treatment of patients with active disease,
  - (d) segregation and custodial care of those not amenable to accepted forms of therapy,
  - (e) adequate rehabilitation
- VI It is to be emphasized that BCG vaccination must not be regarded as a substitute for approved hygienic measures or for public health practices designed to prevent or minimize tuberculous infection and disease. Vaccination should be regarded as only one of many procedures to be used in tuberculosis control
- VII Expansion of modern diagnostic, therapeutic, and rehabilitation facilities is required at this time to make full use of these new methods which can accomplish further dramatic reduction of tuberculosis mortality and morbidity rates in the United States

# THE AMERICAN REVIEW OF TUBERCULOSIS

## ABSTRACTS

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### CLINICAL STUDIES, TUBERCULOSIS

**Avian Tuberculosis**—Up to 1938, there were 13 proved cases of avian tuberculosis in man, 24 others were reported but in them the proof is regarded as insufficient. Adequate proof consists of thorough pathogenicity tests using hens, rabbits, and guinea pigs. In Denmark since 1935, avian tubercle bacilli giving characteristic pathogenicity reactions have been cultured from 6 human cases. Four of the patients had lymphadenitis and one each had pulmonary and meningeal tuberculosis. In 2 cases, cutaneous tests made with avian tuberculin yielded positive results to 0.00002 mg.—*Avian tuberculosis in man, I Gragsted, Lancet, July 16, 1949, 1 123*—(A. G. Cohen)

**Congenital Tuberculosis**—In congenital tuberculosis the infection reaches the fetus either via the umbilical vein or from infected amniotic fluid. The second mode of infection occurs through ingestion of such fluid by the fetus, in which case the primary seat of the disease is the intestinal tract with resultant enlargement of the mesenteric and porta hepatis glands. Some investigators have maintained that an infection from amniotic fluid may be caused by aspiration, this view is doubted by others, there being no definite proof that amniotic fluid enters the lungs. A case of proved congenital tuberculosis occurred in an infant who appeared normal at birth and weighed 8 pounds. The mother was a 31-year-old woman with bilateral pulmonary tuberculosis. On the twenty-second day after birth the child began to take his feedings poorly, he died on the thirtyeth day. Autopsy revealed a generalized, disseminated tubercu-

losis, principally of the glands in the hilum of the liver. The mother died three weeks post partum. Autopsy demonstrated a disseminated tuberculosis particularly of the peritoneum, ovarian tubes, and lungs. It is believed that the infant had a congenital tuberculous infection because (1) the child's extrauterine life was similar to others reported, (2) his tuberculous lesions were commensurate in size and distribution with those following intrauterine infection, (3) the mother had active genital tuberculosis, (4) the child was immediately removed from contact with the mother and there was found no subsequent source of tuberculous infection among the attending staff.—*A case of congenital tuberculosis J. W. Jordan & H. Spencer, Brit M J, February 5, 1949, No 4596 217*—(R. W. Clarke)

**Lupus and Bone Tuberculosis**—Thirty-three patients with lupus were subjected to routine roentgenographic examination of the entire skeletal system. Of these patients, 8 had active bone tuberculosis, 8 others were known to have had bone tuberculosis in the past but it had healed. In addition to these known lesions, roentgenograms revealed latent osseous foci in 20 cases (60.6 per cent). A total of 46 unsuspected bony lesions were discovered. The involvement usually appeared as a circumscribed round or oval area of consolidation in the bony substance, the sizes most frequently encountered were 3 by 5 mm and 4 by 6 mm. These lesions are considered to be of tuberculous etiology.—*Latent bone involvement in patients with lupus (a preliminary report) (Russian), I. N. Grinchar, Probl tuberc, November-December 1948 32*—(V. Leites)

**Coccidioidomycosis and Tuberculosis**—A 21-year-old Japanese-American, who had lived five months in San Joaquin Valley, developed malaise, asthenia, nonproductive cough, a vesicular eruption of the fingers, and acute pleurisy on the left with an effusion. Coccidioidin and tuberculin skin tests were positive. Ten months later an abscess appeared over the sternum. A few months later the following symptoms and signs developed: anorexia, weight loss, headaches, palpable nodules on the scalp, pain and swelling over the dorsum of the left foot, and fever. Acid-fast bacilli were found in the gastric contents. Pus aspirated from the abscess of the foot contained *Coccidioides immitis*. A chest roentgenogram revealed nodular infiltrations in both lungs. Before he died the patient developed multiple abscesses; the pus contained *Coccidioides immitis*. The pathological diagnoses were (1) coccidioidomycosis of the lungs, peritoneum, left shoulder joint, left ankle, skull, and dura, and (2) tuberculosis of the lungs, hilar lymph nodes, liver, spleen, kidneys, peritoneum, adrenal glands, prostate seminal vesicles, sternum, pericardium, and ileum. This is the first case report of coexisting disseminated coccidioidomycosis and disseminated lymphohematogenous miliary tuberculosis.—*Disseminated coccidioidomycosis and lymphohematogenous tuberculosis. Report of a case*, B Hyde & L Hyde, *Arch Int Med*, 1949, 83: 505—(G C Leiner)

**Calciferol for Skin Tuberculosis**—Charpy's regimen of massive oral doses of calciferol has been modified somewhat by the author. The latter recommends more intensive therapy during the first five weeks of treatment, using calciferol 15 mg three times during each of the first two weeks, twice during each of the next three weeks and once weekly thereafter. A salt-free diet is employed on each treatment day and ascorbic acid 500 mg are given daily during the first two weeks. Calciferol therapy is contraindicated in active pulmonary tuberculosis, renovascular disease, hypercalcemia, and senility. The treatment probably increases the defensive ability of the skin in

some unexplained manner.—*Few notes on a modern method of treating cutaneous tuberculosis (Czech)*, J Horáček, *Lekarske listy*, May 15, 1948, 3: 269—(J Ilavský)

**Rib Fracture from Coughing**—Fractures of the ribs resulting from coughing often are recognized but probably are more frequent than the reports indicate. Seven new cases are reported. The mechanism by which the fractures are produced is difficult to determine. Primary tuberculous osteitis is generally believed to be so uncommon that it is unlikely to be the basic cause. A cold abscess arising from an adjacent, caseous gland is a possible explanation. Fractures during coughing have occurred in healthy subjects, possibly associated with an increased fragility of the bones. The apparent high incidence in tuberculous patients suggests an effect of the infection on bony structures but the repeated chest roentgenogram makes it more likely that the lesion will be discovered in these persons. There is no evidence that tuberculous patients are particularly liable to decalcification except in so far as prolonged bed rest may lead to demineralization. The blood calcium concentration is normal in tuberculous patients and fractures heal normally without delay in callus formation. Fractures from coughing seem to occur because the violent, abnormal action, probably associated with asymmetrical posture, produces an uneven tension on the ribs.—*Cough fracture of ribs*, R C Cohen, *Brit M J*, January 22, 1949, 4594: 188—(R W Clarke)

**Cavernostomy**—Of 75 cavernostomies, 67 were performed for cavities persisting after thoracoplasty, 3 for cavities which perforated through the chest wall during thoracoplasty, and 5 for cavities whose closure by thoracoplasty was not attempted. There were 11 deaths (16 per cent), 4 of which occurred in the immediate postoperative period. In this series, 83.5 per cent of the patients were considered "cured" or greatly improved. Contralateral pneumothorax was employed with 9 patients and contralateral thoracoplasty with

one Most of the patients were in poor general condition at the time of operation, 35 subsequently were well and showed complete local healing In 2 of the latter, new cavities appeared and necessitated further rib resections, in 2 others, new cavities were treated with a second cavernostomy Six patients improved greatly and their sputum became negative for acid-fast bacilli although epithelization of the residual opening was slow Nine other patients were greatly improved but had only a short follow-up period The cavity was always localized by tomographic studies and was approached by the axillary route if possible Parenteral and local streptomycin seemed to improve the results The postoperative care was often very prolonged and most of the unsatisfactory results were attributed to the patients' leaving the hospital too early The authors feel that the superiority of their results to those of American surgeons is due mainly to the greater emphasis in France on prolonged and meticulous postoperative care following cavernostomy The procedure is especially indicated in all patients with low respiratory function of the contralateral lung —*Resultats de speleotomie et quelques precisions de technique, A Bernou, L Goyer, Marceaux & J Tricoire, Rev de la tuber, 1949, 13 280 —(V Leltes)*

#### CLINICAL STUDIES, NONTUBERCULOUS DISEASES

**Bauxite-fume Pneumoconiosis**—A fatal pulmonary disease attributable to fumes containing bauxite recently has been discovered, chiefly among furnace feeders and crane operators These men are exposed to dense white fumes during the fusion of finely ground Arkansas bauxite, iron, and coke to produce "corundum," an aluminum-oxide abrasive Clinically the disease is characterized by shortness of breath, cyanosis, substernal discomfort, and recurrent episodes of spontaneous pneumothorax from emphysematous bullae Examination of the chest reveals signs consistent with the parenchymal changes and often with pneumothorax Roentgenographic

changes are distinctive and quite different from those seen in other pneumoconioses The cardinal features are diffuse, irregular, lace-like and granular shadows, greatly increased width of the mediastinum and collapse of the lung In 6 fatal cases the specific pathological findings were confined to the lungs Grossly there was diffuse, widespread induration without nodulation, large, emphysematous vesicles were frequent, often reaching a giant size The hilar nodes were neither enlarged nor hard and were completely free of nodulation Microscopically the lungs always showed diffuse fibrosis, the result of hyalinization of the alveolar walls, doubly refractile particles frequently were demonstrated by polarization microscopy The causative fumes consist principally of amorphous material in particles not greater than  $0.5\ \mu$  in diameter These fumes have an average silica content of 36 per cent and alumina content of 50 per cent The ashed residue of lungs from fatal cases contained 27 per cent silica and 33 per cent alumina This affords some evidence that the amorphous alumina dust is the dominant etiological agent since no human disease has yet been ascribed to silica particles as small as those in the fumes It is still undetermined whether silica plays an active but adjunctive role in the production of this disease—*The morphology of bauxite-fume pneumoconiosis, J P Wyatt & A C R Riddell, Am J Path, May, 1949, 25 447 —(J S Woolley)*

**Circumscribed Bronchitis**—Circumscribed bronchitis as a clinical entity was recognized in the course of bronchoscopic examinations It usually involves the stem bronchi and the first few centimeters of the lobar bronchi, especially those of the lower lobes, being chiefly unilateral The findings are those of mucosal inflammation of varying degree, the main feature of which is its circumscribed character Swelling of the mucosa was frequent and was present in 50 per cent of the cases Redness, hypersecretion, and increased sensitivity to cough-producing stimuli also were found The diagnosis was made because

the symptoms suggested more serious involvement so that bronchoscopy was performed. In the 50 cases diagnosed as circumscribed bronchitis, bronchoscopy was done for the following reasons: hemoptysis (22 cases), persistent cough (6 cases), marked dyspnea (8 cases), abnormal expectorations (14 cases). In some cases, tissue was removed and showed only simple inflammatory changes. A few bronchoscopic applications of adrenalin to the involved area produced a rapid improvement or cure. The development of an increased cough reflex in a circumscribed part of the bronchial mucosa is believed to be the basis of the condition but the etiology is admittedly obscure.—*La clinique des bronchites circonscrites*, J M Lemoine & J de Léobardy, *Presse méd*, May 7, 1949 404 —(V Leites)

**Toxic Effects of Pontocaine**—Amethocaine hydrochloride (Pontocaine) can produce severe toxic reactions, 12 deaths have been reported following its use before bronchoscopy and gastroscopy. Such deaths are the result either of sensitivity or of overdosage and present the classic picture of cocaine poisoning. Amethocaine is ten times more potent than procaine or cocaine, is quick acting, and has a prolonged effect. It also is more toxic than cocaine. Amethocaine penetrates the tissues more rapidly than cocaine and does not produce vasoconstriction so that adrenalin must be used with it. The following prophylactic measures are suggested: premedication with barbiturates, administration of an amethocaine pastille thirty minutes before the examination, addition of adrenalin 1:1,000 solution in the proportion of 4 to 1 by volume, limitation of the total dose of amethocaine to 4 cc of a 2 per cent solution, avoidance of the use of the laryngeal spray. The drug should not be applied to an inflamed, traumatized, or highly vascular surface. To control a toxic reaction, an unobstructed airway must be secured by an endotracheal tube if necessary, artificial respiration should be given with an oxygen-carbon-dioxide mixture, a rapidly acting barbiturate may be injected intravenously and

respiratory and cardiac stimulants administered.—*Amethocaine hydrochloride: Severe toxic effects when used for bronchoscopy*, C A Jackson, *Brit M J*, January 15, 1949, No 4593 99 —(R W Clarke)

**Spontaneous Rib Fracture**—A 63-year-old white man with bronchial asthma, severe cough, dyspnea, and pain in the right chest was found to have spontaneous fractures of the eighth, ninth, and tenth ribs on the right side. Another roentgenogram taken several months later showed callous formation over these fractured ribs. It was felt that the opposing action of two sets of muscles is necessary to produce this type of fracture. A contraction of the serratus anterior, which exerts a pull laterally and cephalad as opposed to the simultaneous pull of the external abdominal oblique medially and caudad, is the most likely cause. Spontaneous rib fracture occurs only rarely in bronchial asthma.—*Spontaneous rib fracture in bronchial asthma*, M L Gelfand, *Ann Allergy*, March-April, 1949, 7 217 —(L Hyde)

**Rib Fracture from Coughing during Pregnancy**—Rib fracture due to coughing occurred during late pregnancy in 4 women, none of whom was known to have fragile bones. Slight osteoporosis was found in only one patient, all 4 had blood calcium and phosphorus concentrations within normal limits. Such fractures usually produce a severe, sharp pain during a fit of coughing. The sensation often is described as that of something "giving" or "cracking" in the chest. A mild fever may follow and a pleural rub occasionally is noted. A localized area of tenderness is present on one or more ribs. The ninth, tenth, and eleventh ribs are the most likely sites of the fractures and they are more frequent on the left side. The mid-thoracic fractures occur along the interdigitation of the external oblique and anterior serratus muscles and are assumed to be the result of shearing stress. The likelihood of fracture is reported to be increased if the serratus is taut at the time of coughing as it may be when the arm is raised or when the

patient is resting on one elbow. From this study it seems likely that fractures of the lower ribs are caused by the shearing stress of the external oblique and the costal slips of the latissimus dorsi. The posture of late pregnancy also may play a part. Another possible cause is the driving of the uterine mass backwards and upwards against the inner surface of the lower chest by contraction of the anterior abdominal muscles in coughing. This force would be deflected to the left by the liver. Although a fractured rib is a trivial injury, it can produce extreme discomfort and insomnia. The importance of recognizing the fracture lies in the great relief afforded by early and adequate strapping of the chest. Equally important is the avoidance of tiresome confinement to bed and needless investigation, often in a hospital.—*Cough fracture in late pregnancy*, J W Paulley, D H Lees, & A C Pearson, *Brit M J*, January 22, 1949, No 4594 135—(R W Clarke)

**Spontaneous Mediastinal Emphysema**—Two cases of spontaneous pneumomediastinum developed during labor associated with severe straining. The clinical course in each case was uneventful with recovery in a few days. In differentiating the condition from pneumopericardium, the important points are the presence of air in the neck, the milder symptoms and, in the roentgenogram, the air along the left cardiac border extends above the level of the pericardial sac.—*Spontaneous pneumomediastinum in pregnancy*, D J MacRae, *Lancet*, May 21, 1949, 1 902—(A G Cohen)

**Spontaneous Mediastinal Emphysema**—A woman in her eighth month of pregnancy developed spontaneous mediastinal emphysema during an asthmatic attack. The diagnosis is simple if subcutaneous emphysema appears. Otherwise, two important diagnostic features are (1) an auscultatory crunch during cardiac systole (Hamman's sign), and (2) the presence in roentgenograms of radio-opaque lines running parallel to the vertebral

column in line with the tips of the transverse processes and of a narrow area of translucency between them and the root shadow, representing air pockets lining the lateral boundaries of the mediastinum.—*Acute mediastinal and subcutaneous emphysema*, L Fridjohn & P G Azzopardi, *Lancet*, May 24, 1949, 1 904—(A G Cohen)

**Bronchogenic Carcinoma**—Phalangeal metastases from any carcinoma are rare. Three cases of metastases to the phalanges from bronchogenic carcinoma are reported. In all 3, the lesions at first seemed to be inflammatory but roentgenograms showed bone destruction. Aspiration biopsy was diagnostic in 2 of the cases.—*Phalangeal metastases in bronchogenic carcinoma*, G M Colson & A Willcox, *Lancet*, January 17, 1948, 1 100—(A G Cohen)

**Surgical Treatment of Bronchiectasis**—Since the introduction of aerosol penicillin, the patients come to the operating room with "dry lungs." Bronchoscopy is not done in the immediate preoperative period, it results in the patients becoming poor anesthetic subjects. Simple anesthetic procedures are practised. A small amount of sedative medication is given two hours before operation. Anesthesia is induced with intravenous pentothal. A mixture of nitrous oxide and oxygen in a ratio of 3:1 is then given for a few minutes before ether is added. When light anaesthesia is obtained, the trachea is intubated with a short Magill endotracheal catheter. A slow infusion of citrated blood is started. The patient is placed in a lateral position and draped in a manner which allows the anesthesiologist an unobstructed view of the operative site. A few minutes before the pleura is entered, positive pressure is built up to 5 or 6 mm of mercury. This prevents rapid collapse of the exposed lung. Later, this pressure is gradually lowered. The tracheobronchial tree is aspirated frequently with a catheter 45 cm long. The anesthesiologist watches the diaphragm closely, jerky movements are the earliest sign of tracheobronchial obstruction.

or mediastinal flutter Aspiration is then performed, if this does not help, the pressure is built up to 4 or 5 mm of mercury Every half hour the surgeon pauses for one to two minutes while the unoperated lobes are re-expanded Thus, inadvertent ligation of uninvolved bronchi is detected Blood is given according to the amount lost, this averages 1,000 to 1,500 cc After the diseased lung has been removed, the tracheobronchial tree is aspirated The remaining portion of the lung is then re-expanded slowly The anesthetists engaged in major thoracic surgery should be able to pass a bronchoscope with the patient lying in a lateral position After the chest is closed, the patient is turned on his back and water bottles are attached to the drainage tubes The bronchoscope is then passed and a vigorous stream of oxygen is sent through it Roentgenograms of the chest are taken while the patient is still in the operating room The patient remains until the films are developed If these show persistent collapse, then bronchoscopy is repeated—*Anesthesia in the surgical treatment of bronchiectasis, L H Mousel, New England J Med, January 29, 1948, 238 148—(A G Cohen)*

#### ANTIMICROBIAL THERAPY

**Streptomycin for Tuberculous Meningitis**—In the Salpêtrière Hospital in Paris 147 children with tuberculous meningitis were treated in the course of two years The over-all recovery rate was only 29.2 per cent, but in the beginning many cases arrived for treatment in a desperate state During the follow-up period of four to twenty months, none of the recovered patients exhibited any sequelae Of the patients with meningitis alone, 33 per cent recovered, of those with meningitis associated with milary tuberculosis, 25 per cent survived There were no survivors among the patients in whom meningitis occurred as a later complication of milary tuberculosis Results have improved during the past two years with modification of the treatment In the beginning streptomycin was administered discontinuously, the patients receiving 2 or

3 series lasting one month each Only a small number of intrathecal injections were given On this regimen, 17.5 per cent of the cases were arrested At present treatment is continued until the spinal fluid cell count is less than 10 Children rarely relapse after the cell count reaches this level Daily intrathecal injections are given during the first month The dosage was 20 Gm twice daily intramuscularly and 12 to 50 mg intrathecally The percentage of recoveries in this series was 47.5 per cent The administration of streptomycin together with a sulfone compound raised the recovery rate further to 59 per cent in a series of 18 patients—*Résultats de 2 ans de traitement de la méningite tuberculeuse de l'enfant, M J Fouquet, V Heimann, M Meyer & Hennequet, Presse méd, April 23, 1949, 57 372—(V Lentes)*

**Streptomycin for Tuberculous Meningitis**—Of 76 admissions for tuberculous meningitis, 67 patients proved to have the disease, the remaining 9 had suggestive symptoms but the diagnosis was not substantiated Prompt diagnosis is important, mental apathy being an early sign In 3 patients the cerebrospinal fluid was normal early in the disease When they occur, a fall in sugar, a rise in protein, and pleocytosis of the fluid are important diagnostic signs Acid-fast bacilli were seen in the cerebrospinal fluid from 39 patients (58 per cent) prior to and within 48 hours of admission Tubercle bacilli were recovered by culture or guinea pig inoculation of the fluid in 58 cases (87 per cent) Diagnosis by one or both of these criteria was established in 62 cases (92 per cent) The Mantoux test was positive in 50 of 51 patients tested, chest roentgenograms showed abnormalities in 50 of 66 patients Forty patients received combined intrathecal and intramuscular streptomycin, 15 (37 per cent) of them survived Ten others received intramuscular therapy only and 2 survived Four patients received intramuscular therapy followed by combined therapy, one survived Important factors contributing to therapeutic failure are vascular changes in the brain and hydrocephalus

In 10 patients, a tube was inserted into the lateral ventricle to relieve the intracranial fluid pressure, only one of these patients survived. Strains of *M. tuberculosis* isolated from 43 of the patients have shown no resistance to streptomycin. Of the entire series, 18 patients (33 per cent) survived with complete clinical recovery in 16. Two have had relapses and show definitely abnormal cerebrospinal fluid—*Tuberculous meningitis*, J. Rubin & A. F. Mohun, *Brit. M. J.*, February 26, 1949, No. 4599, 535—(R. W. Clarke)

**Streptomycin for Enteric Tuberculosis**—The rapid effect of streptomycin on the clinical symptoms and roentgenological changes of intestinal tuberculosis was demonstrated in 8 cases. Complete regression or very marked improvement was noted in all but one patient who died of a pulmonary hemorrhage while under treatment. Four to six weeks of treatment with streptomycin in daily doses of 1.5 to 2 Gm. were sufficient to produce the desired result. However, the pulmonary pathology often necessitated longer administration—*Efficacité de la streptomycine sur la tuberculose intestinale*, P. Damade, F. Pichaud, F. J. Traissac, P. Fricour, & M. Roux, *Rev. de la tuberc.*, 1949, 13, 535—(V. Leites)

**Streptomycin for Bone and Joint Tuberculosis**—The use of streptomycin for bone and joint tuberculosis was investigated by various French clinics under the auspices of the Ministry of Health. About 300 patients with proved tuberculous lesions which were not improving have been under treatment for six to ten months. Local and general treatment was continued and streptomycin was given in daily doses of 1.0 Gm. for adults, 0.25 Gm. for children below the age of five, and 0.5 Gm. for children five to fifteen years of age. Treatment was continued for 120 days during which no other chemotherapeutic agent was given. The reports show that (1) An extremely favorable effect of streptomycin on the general condition and on constitutional symptoms was often noted. It was sometimes dramatic

in severely cachectic patients (2) The healing of fistulas was usually successful. Fistulas which had drained as long as nineteen years closed rapidly (3) The effect on cold abscesses was less constant. Some observers reported no success, others had favorable results in a few patients after prolonged treatment (4) No definitive conclusions were reached on the effect of streptomycin on the course of the osteoarticular lesions. It was felt by most observers that streptomycin had a rapid effect if given early, before bone destruction, more advanced lesions required surgery. Necessary operations were simplified by the preoperative administration of streptomycin and cases previously considered too far advanced for intervention were operated upon successfully after treatment. Lesions treated with streptomycin sometimes were found bacteriologically sterile at operation. There was also a favorable effect on the postoperative course—*Streptomycine et tuberculose ostéo-articulaire*, M. E. Sorrel & Sorrel-Dejerine, *Premiers résultats de l'emploi de la streptomycine dans le traitement des tuberculoses ostéo-articulaires*, E. Bernard, P. Padavan & A. Lotte, *Dix mois de streptomycine dans les localisations ostéo-articulaires de la tuberculose*, P. Gerard-Marehand, *Premiers essais de traitement des tuberculoses ostéo-articulaires par la streptomycine*, P. Ingelrans, A. Vendeuvre & J. Nigoul, *Streptomycine et évolution de la tuberculose osseuse*, M. Galland, *Effets immédiats d'un traitement de quatre mois par la streptomycine sur les tuberculeux osseux et ganglionnaires*, R. Serée, H. Dettloff, P. Hubert & H. Verney, *Le traitement des tuberculoses chirurgicales par la streptomycine*, J. Bashde, J. Arrighi de Casanova, P. Roussel, Monfajon, Ch. Albaret, *Semaine d'hôp. Paris*, May 10, 1949, 25, 1491—(V. Leites)

**Streptomycin with Extrapleural Pneumothorax**—Extrapleural pneumothorax was performed in 65 patients in 1947 and 1948, 32 of them receiving streptomycin preoperatively. The others were operated upon before streptomycin became available. In the streptomycin-



treated group there was one case of tuberculous effusion whereas in the untreated group tuberculous effusions occurred in 15 cases. The patients who developed fluid in the extrapleural space were subsequently treated with local injections of streptomycin 1.0 Gm daily for 15 to 20 days. In 10 cases of the 15, there was complete absorption of fluid. In the remaining 5 cases, the fluid became sterile and serofibrinous after a few weeks.—*Les épanchements purulents tuberculeux des P N E P et streptomycine, Le Foyer, Bertheau, Pervès & Sabiani, Rev de la tuberc, 1949, 13: 129*—(V Leites)

**Streptomycin and Surgery**—The indications for the use of streptomycin in association with the surgical treatment of pulmonary tuberculosis are divided into 6 groups: (1) Acute pneumonic or bronchopneumonic cases as well as subacute cases with extensive nodular dissemination are at the onset strictly "medical" cases. If streptomycin is effective, these cases may become eligible for surgery in order to control remaining cavitory lesions. (2) Many chronic cavitory cases are unacceptable for surgery because of contralateral disease. These may be good surgical risks after regression of the contralateral lesions following streptomycin. (3) In some cavitory cases surgery is prevented by a very unfavorable clinical course with fever, weight loss, and abundant expectoration. Streptomycin may "cool off" the process and reduce expectoration so that surgery can be performed with a gain in time and safety. (4) In uncomplicated cases with none of the above mentioned contraindications to thoracoplasty, routine administration of streptomycin is not felt to be indispensable and, if decided upon, the course should not exceed two weeks. The routine use of streptomycin is more justified before extrapleural pneumothorax. (5) Preoperative and postoperative treatment with streptomycin is recommended as a routine procedure in excisional surgery. (6) Streptomycin has been of great help in such postoperative complications as extension of the tuberculous process in the lung, tubercu-

lous extrapleural effusions, and chest wall fistulas.—*Sur les indications diverses et les modalités d'emploi de la streptomycine en association avec la collapsothérapie chirurgicale, E Bernard, A Lotte, J Weill, R Monod, Mathey & Monod, Rev de la tuberc, 1949, 13: 1*—(V Leites)

**Streptomycin Resistance of Tubercle Bacilli**—Tubercle bacilli from 39 patients were tested for streptomycin resistance before, during, and after treatment of the patients for 90 to 180 days with streptomycin 1 Gm daily in two doses twelve hours apart. None of the 32 strains tested was resistant to 2.5  $\gamma$  per cc. At the end of 30 days of treatment, no resistant strains were found in any of 30 patients. At the end of 60 days, 13 per cent of 24 patients had resistant bacilli. After 90 days, 29 per cent of 28 patients, and after 100 to 120 days, 45 per cent of 31 patients, had streptomycin-resistant strains. The number of resistant bacilli increased after cessation of treatment in 4 patients. It would seem advisable, therefore, to postpone final decision on the number of strains which become resistant until several months after the completion of streptomycin therapy. The average serum concentration of streptomycin was found to drop rapidly from 33  $\gamma$  per cc at two hours to 8.6  $\gamma$  per cc at eight hours and then more slowly to 1.7  $\gamma$  per cc at twelve hours after injection.—*Resistance of the tubercle bacillus to streptomycin, B Blattberg & H Ehrhorn, J Lab and Clin Med, March, 1949, 34: 358*—(F G Petrik)

**Bacterial Reaction with Streptomycin Therapy**—In a series of 300 patients treated with streptomycin, 20 developed nausea, abdominal distention, vertigo, tachycardia, fever, and leukocytosis during the third or fourth week of treatment. When penicillin was given in addition to the streptomycin, all symptoms promptly disappeared. This reaction is neither an allergic nor a toxic one. It is due to a decided increase in the number of fecal streptococci.—*Streptococcus fecalis reaction occurring during streptomycin therapy,*

W W Stewart & O L Baldrige, *J A M A*, February 26, 1949, 139: 579 —(H Abeles)

**Streptomycin for Respiratory Infections** — Streptomycin was given to 50 patients with various infections of the respiratory tract. Strikingly beneficial effects were obtained in 7 patients with pneumonia due to *K pneumoniae*. Good results were seen in 3 patients with pneumonia due to *H influenzae* and in 3 cases of pulmonary tularemia. There may have been some beneficial effect in one of 2 patients with coccid pneumonia. There was a questionable effect in 2 cases of pertussis with bronchopneumonia. One patient treated with streptomycin and penicillin survived pneumonia with agranulocytosis. There was no effect from the streptomycin treatment in one patient with atypical pneumonia and good response in one patient with virus pneumonia and a secondary *P aeruginosa* infection. No effect was seen in 3 cases of asthma with chronic infection of the upper respiratory tract, in 6 cases of chronic bronchitis, nor in 8 cases of bronchiectasis. One case of actinomycosis showed a good response temporarily, sustained improvement was obtained in one patient with blastomycosis, no effect was seen in one patient with moniliasis. No effects from the streptomycin treatment were seen in 6 cases of sarcoidosis, 2 cases of Hodgkin's disease, nor in one case of silicosis. —*Streptomycin. Reports of its clinical effects in forty-four patients treated for various infections of the respiratory tract*, E J Pulaski & Th T White, *Arch Int Med*, September, 1948, 82: 217 —(G C Leiner)

**Tuberculostatic Effect of Furacin** — A bacteriostatic effect of furacin on virulent human tubercle bacilli *in vitro* occurred with a concentration of 1:20,000 (5 mg per 100 cc) and a bactericidal effect with 1:5,000 (20 mg per 100 cc). However, the furacin, in the maximum tolerated dose of about 35 mg per Kg daily for 64 days, did not appreciably affect the course of tuberculosis produced in guinea pigs by the H37Rv strain. Resistance to furacin *in vitro* was not evident after many

transfers of the H37Rv culture in drug-containing medium. The combination of Furacin and streptomycin in Tween-albumin liquid medium delayed, but did not prevent, the development of streptomycin-resistant bacilli of the H37Rv strain. —*Tuberculostatic effect of furacin in vitro and in vivo*, E Wolinsky, V Wetzel, & W Steinhilber, Jr, *Proc Soc Exper Biol & Med*, March, 1949, 70: 488 —(F B Schibert)

**Aureomycin for Primary Atypical Pneumonia** — A controlled series of 22 patients with primary atypical pneumonia were treated with aureomycin. Treatment was instituted with an intravenous injection of aureomycin hydrochloride 50 mg and an oral dose of aureomycin 1.0 Gm. Thereafter, each patient received aureomycin 1.0 Gm every six hours until his temperature had been normal for at least 48 hours. Nausea and vomiting were frequent after oral administration of the drug but never followed an intravenous injection. All patients responded uniformly well, defervescence was extraordinarily rapid in the majority. Relapse occurred in 3 patients after treatment was stopped and aureomycin was as effective in treating the relapse as the initial episode. A control group of 20 patients was treated with penicillin, prompt recovery occurred in almost half of this group. Aureomycin treatment resulted in the prompt recovery of all patients and it can be considered highly effective in primary atypical pneumonia. —*Aureomycin in primary atypical pneumonia. A controlled evaluation*, G Mehlhorn & R I Shragg, *J A M A*, May 28, 1949, 140: 391 —(H Abeles)

**Aureomycin for Tularemia** — Three patients with tularemia were treated with aureomycin. They responded promptly and the results are comparable to streptomycin therapy in the degree of effectiveness. —*Aureomycin in treatment of experimental and human tularemia*, T E Woodward, W T Raby, W Eppes, W A Holbrook & J A Hightower, *J A M A*, March 26, 1949, 139: 830 —(H Abeles)

## LABORATORY STUDIES

**Thiosemicarbazone in Experimental Tuberculosis**—The effect of a thiosemicarbazone, TB 1 698, prepared by Domagk and his collaborators in Germany, was studied in experimental tuberculosis of mice. Doses of 10 mg were given orally for 46 days after intravenous infection with 1 mg of a three-week-old culture of virulent tubercle bacilli. An untreated group of mice infected in the same manner served as controls. In the untreated group, all the animals died in 26 to 30 days. In the treated group, 41 per cent of the animals survived until the fifty-eighth day, when they were sacrificed. There was a marked decrease in the bacillary content of the lungs in the treated mice as compared to the untreated ones. The microscopic character of the lesions in the treated animals resembled that seen with streptomycin therapy but neither the length of survival nor the signs of healing were as good as those with streptomycin. The incidence of relapses was very high in spite of continuation of the daily treatment. The drug seemed to have its maximum antimicrobial effect at the onset of treatment and the proliferation of tubercle bacilli was marked after the forty-fifth day. The mode of action of thiosemicarbazone is considered analogous to that of p-aminosalicylic acid but its effectiveness seems to be higher.—*Effets curatifs du Thiosemicarbazone (TB 1) dans la tuberculose expérimentale de la souris*, C. Levaditi, *Presse méd*, June 11, 1949, 57: 519.—(V. Leites)

**Nutrition and Response to Tuberculosis**—A controlled study was made of the physiological and pathological responses of protein-deficient rats to a tuberculous infection. The growth, food consumption, plasma proteins, hematologic variations, and tissue response were investigated. Young, growing rats were maintained on one of 3 diets: adequate, protein-deficient, or initially adequate and then acutely, severely deficient. Infection of these animals with *M. tuberculosis* H37Rv gave results which seem to favor the concept that dietary protein deficiency does not alter sig-

nificantly the susceptibility of the rats nor the course of the tuberculosis. This seems to be true regardless of the severity or duration of the protein deficiency; it apparently makes no difference whether the previous protein intake was high or low. Changes in the white blood cell count, hemoglobin and plasma proteins were consistent with those in uninfected, protein-deficient rats and were not peculiar to the tuberculous animals. There were equal changes in the myeloid-erythroid ratio of the marrow in infected animals. Tuberculous rats had an apparent increase in the alpha and beta globulins but this was not evident when the unit-circulating quantities of the plasma components were estimated.—*Nutritional status and infection response. II. Electrophoretic, circulating plasma protein, hematologic, hematopoietic, and pathologic responses to mycobacterium tuberculosis (H37Rv) infection in the protein-deficient rat*, J. Metcalf, D. Darling, D. Wilson, A. Lapi & F. J. Stare, *J. Lab. & Clin. Med.*, March, 1949, 34: 335.—(F. G. Petrá)

**Test of Streptomycin Sensitivity**—Rapid evaluation of streptomycin sensitivity is possible by direct culture of the pathological specimen on solid and liquid media containing graduated concentrations of streptomycin. Incipient growth can be demonstrated as early as on the fifth or sixth day by microscopic examination of slides obtained from the inoculated media. This method may not be absolutely accurate but it is considered adequate and valuable for clinical purposes.—*Évaluation rapide de la streptomycine résistance par la culture directe des produits bacillifères*, J. Bretey, P. J. Colletos & H. Boissert, *Ann. Inst. Pasteur*, February, 1949, 76: 188.—(V. Leites)

**Streptomycin-dependent *M. Ranae***—A new streptomycin-dependent variant of *Mycobacterium ranae* has been isolated. It will grow only in low concentrations of streptomycin. Parent-type cells which grow without streptomycin were isolated from several streptomycin-dependent strains. The number of parent-type cells found varied with the size

and character of the population and with the concentration of streptomycin in which the dependent cells were growing. Detailed studies failed to reveal any differences between the parent-type cells found in the streptomycin-dependent cultures and the cells of the original parent population. This is believed to be an example of reverse mutation. Attempts to induce changes in the incidence of parent-type cells in streptomycin-dependent populations were unsuccessful. Streptomycin-dependent and streptomycin-resistant cells were grown in the same culture and after several successive subcultures the presence of streptomycin-dependent cells could not be readily detected. — *The biological characteristics of streptomycin-dependent Mycobacterium ranae*, D Yegran & R J Vanderlinde *J Bact*, February, 1949, 57 169 — (F G Petrik)

**Culture of Tubercle Bacilli** — The addition to the medium of relatively small amounts of horse serum (1:30) modifies considerably the cultural characteristics of tubercle bacilli. In the simple Sauton medium, tubercle bacilli grow very poorly in the depth of the medium and have a tendency to develop on the surface. Under the influence of serum, the tubercle bacilli become more anaerobic and grow in the depth of the liquid medium as early as the sixth day after inoculation with a small number of bacilli. In the presence of serum this growth in the depth takes place either in the presence or absence of glycerine. Sauton medium with horse serum has proved very useful and inexpensive for titration of certain antibiotics, the results being comparable to those obtained with the media of Dubos and Youmans. — *Culture en profondeur de bacille tuberculeux en milieu de Sauton additionné de sérum de cheval et titrage de certains antibiotiques* J Solomondès, *Ann Inst Pasteur*, April, 1949, 76 371 — (V Leites)

**Transfer of Systemic Tuberculin Sensitivity** — Systemic tuberculin sensitivity could be passively transferred in guinea pigs by means of the cells of induced peritoneal exudates from tuberculous donors. The systemic shock

induced in these recipients was of the typical delayed tuberculin type. Desensitization of some tuberculous donors with tuberculin abolished the capacity of their peritoneal cells to passively transfer the tuberculin sensitivity. This evidence indicates that desensitization results from the saturation of fixed cellular antibody with antigen. — *Tuberculin reaction. III. Transfer of systemic tuberculin sensitivity with cells of tuberculous guinea pigs*, W F Kirchheimer, R L Weiser, & R Van Liew, *Proc Soc Exper Biol & Med*, January, 1949, 70 99 — (F B Seibert)

**Leukocyte Blockade of Tuberculin Cytolysis** — Suspensions of white blood cells from normal persons with a negative intracutaneous tuberculin reaction, as well as those from patients with active tuberculosis, adsorbed tuberculin (OT) from the plasma. The tuberculin was assayed by its *in vitro* cytotoxic effect on the white blood cells of tuberculous subjects. White blood cells from normal or tuberculous mice did not adsorb tuberculin. Plasma from patients with active tuberculosis partially inactivated tuberculin whereas normal human plasma did not. *Leukocyte blockade of in vitro tuberculin cytotoxicity*, C B Favour, *Proc Soc Exper Biol & Med*, February, 1949, 70 369 — (F B Seibert)

**Pulmonary Edema due to ANTU** — Dogs under nembutal anesthesia were given alpha-naphthyl thiourea (ANTU) intravenously in propylene glycol. When one cc per Kg of a 2 per cent solution was injected, the animals developed fatal pulmonary edema. The first evidence of changes leading to edema was an increase in the flow of lung lymph. Greater rate and minute volume of breathing followed. Blood gas analyses indicated that the hyperpnea of rapidly developing pulmonary edema was peripheral in origin. — *Acute effects upon the lungs of dogs of large intravenous doses of alpha naphthyl thiourea (ANTU)*, C K Drinker & E Hardenbergh *Am J Physiol*, January, 1949, 156 55 — (G C Leiner)

**Pulmonary Edema and Intracranial Pressure**—Increased intracranial pressure was produced in 24 guinea pigs five minutes before they were guillotined. In approximately one-half of them pulmonary edema, congestion, and hemorrhage were found, and the lung weight/body weight and lung weight/heart ventricle weight ratios were elevated. Bilateral cervical vagotomy exerted a protective effect against pulmonary edema subsequent to elevation in intracranial pressure.—*Pulmonary lesions in guinea pigs with increased intracranial pressure, and the effect of bilateral cervical vagotomy*, G S Campbell & M B Visscher, *Am J Physiol* April 1949, 157 180—(G C Leiner)

**Fluid Shifts in Pressure Breathing**—A method has been developed for exposing anesthetized animals to high positive pressure respiration, using a counter-pressurization system and a simple helmet. Animals exposed to pressure breathing show a rapid loss of fluid from the circulation which is roughly proportional to the mean respiratory pressure employed. Protein leakage was inconstantly observed in animals exposed to pressure breathing.—*Fluid shifts in animals during pressure breathing*, Ch Mann & J Goodman, *Am J Physiol*, October, 1948, 155 208—(G C Leiner)

**Respiration after Pulmonary Artery Ligation**—From experiments in dogs in which the left pulmonary artery had been ligated the following conclusions were made: "A lung with a ligated pulmonary artery can maintain a respiratory function. The capacity of such a lung to absorb oxygen gradually increases over a period of months. When oxygen rather than air is supplied through a bronchspirometric cannula, while the intact lung continues to breathe air, the oxygen content of the arterial blood is found to rise. The effective flow in the bronchial arteries of such a lung increases with time after ligation, as measured by bronchspirometry and an application of the Fick principle. The increase in circulation is in step with the expansion of

the vascular bed demonstrated in anatomical studies by the vinylite method as reported elsewhere. This flow is largely a burden on the left heart whose output becomes roughly one-third greater than that of the right. A similar situation obtains in human disease, such as bronchiectasis or congenital pulmonic stenosis, where there is an extensive collateral circulation to the lungs."—*Respiratory function and blood flow in the bronchial artery after ligation of the pulmonary artery*, W E Bloomer, W Harrison, G E Landskog, & A A Loeblow, *Am J Physiol*, May, 1949, 157 317—(G C Leiner)

**Pulmonary Infarction**—Obstruction of branches of the pulmonary artery results in infarction only when there is interference with the collateral circulation at the same time. Pulmonary embolisms were produced in dogs by releasing blood clots from the jugular veins; no infarctions developed. Pulmonary congestion was produced in 8 dogs by the intravenous administration of alpha-naphthylthiourea prior to the release of emboli; 3 developed pulmonary infarction distal to the embolism and 4 had alveolar hemorrhage distal to the embolism.—*Experimental pulmonary infarction. Abnormal pulmonary circulation as a prerequisite for pulmonary infarction following an embolism*, D W Chapman, L J Gugle & P W Wheeler, *Arch Int Med*, February, 1949, 83 168—(G C Leiner)

**Resuscitation from Obstructive Asphyxia**—Obstructive asphyxia was produced in dogs and different methods for resuscitation were tested. When no treatment was given, 32 per cent of 22 dogs survived. Of 20 dogs given manual artificial respiration in air, 35 per cent survived. When mechanical artificial respiration in air was used, 75 per cent of 20 dogs survived. With mechanical artificial respiration and 100 per cent oxygen, 71 per cent of 21 dogs survived. When mechanical artificial respiration was used with a mixture of 7 per cent CO<sub>2</sub> and 93 per cent O<sub>2</sub>, 85 per cent of 20 dogs survived.—*Resuscitation from obstructive asphyxia*, H Schuerma, A C Iv,

W L Burkhardt & A F Thometz, *Am J Physiol*, February, 1949, 156 145—(G C Leiner)

**Experimental Pulmonary Atelectasis**—Atelectasis occurs in a part of the lung when the bronchus leading to it is completely occluded as happens frequently during various pathological processes. In such cases the air in the occluded segment is resorbed. Atelectasis also occurs when a bronchus is partially occluded by an obstacle which acts as a valve permitting expiration from, but not inspiration into, a part of the lung. In this circumstance, air is both expired and absorbed. Lesions which act in this fashion are very rare, more often the obstacle in the bronchus permits inspiration but no expiration so that emphysema results. Collapse therapy as used in the treatment of pulmonary tuberculosis seeks to reduce the air content of cavities and to produce atelectasis of the surrounding lung parenchyma. Anything which induces emphysema or prevents drainage of secretions from the collapsed area interferes with the treatment. Experimental pulmonary atelectasis was produced in dogs by the authors who introduced a metal check valve through the Chevalier Jackson bronchoscope into the bronchus of one lower lobe. The valve used permitted both the expiration of air and the evacuation of bronchial secretions from beyond the obstruction. The resultant atelectasis did not produce signs on physical or roentgenographic examination although the area was demonstrable at post-mortem examination. When the valve was inverted, emphysema resulted but this also was demonstrable only by dissection. These results suggest a means of producing therapeutic localized atelectasis with free drainage of secretions. There are many technical difficulties, however, especially when the attempt is made to occlude an upper bronchus. Some means of decreasing the reaction of the bronchial tissue to the foreign body were found and are being studied further.—*Experiment atelectasis of the lungs by bronchial obstruction* (Slovak), Z Scheiner &

M Cara, *Rozhledy v Tuberculose*, 1948, 8 94—(J Ilavsky)

**Gas Exchange in Respiratory Dead Space**—In 2 healthy adults, air samples from the supraglottic portion of the respiratory dead space were analyzed. Within one to two seconds during breath-holding after the end of an inspiration, a small rise in carbon dioxide tension and fall in oxygen tension were found. When the breath was held at the end of an inspiration for progressively longer periods, the carbon dioxide concentration increased at a nearly steady state, whereas the oxygen concentration fell only during the first ten seconds. It is believed that the gas exchange occurs across the mixed glandular secretions which bathe the supraglottic area.—*Study of the exchange of oxygen and carbon dioxide in the supraglottic portion of the respiratory dead space*, M Galdston & S A Horowitz, *Am J Physiol*, December, 1948, 155 420—(G C Leiner)

**Artificial Respiration and Altitude**—Five types of artificial respiration were evaluated in rats at Denver's altitude and at an altitude of 40,000 feet. The types studied were Eve tilt board, Schafer prone pressure, Pulmotor or 'suck and blow' type, Drinker respirator, and Thunberg barosprator. At high and low altitudes the mechanical methods for artificial respiration were superior to manual methods. The Schafer method was more effective than the Eve method. The administration of oxygen while giving artificial respiration at high altitudes proved especially beneficial to the circulation. This was particularly true with the barosprator which was the most effective method studied for restoring the circulation. Since the circulatory response always occurred first, this was important in bringing about the resumption of respiration. Low temperatures had a better effect than the administration of oxygen. Carbon dioxide mixtures. Coramine proved effective in stimulating respiration at low altitudes but not at high. Strychnine also was effective, but caffeine, picrotoxin, metrazol,

and potassium cyanide had little effect — *Efficiency of various types of artificial respiration at high altitudes, F R Blood & F E D'Amour, Am J Physiol, January 1949, 156 52* — (G C Leiner)

**Carbonic Anhydrase in Blood** — With a new method, measurements of carbonic anhydrase activity of the blood were made in 40 patients with dyspnea due to cardiac or pulmonary diseases, and in one patient with obstruction of the superior vena cava. The anhydrase activity always was normal in relation to hematocrit value, erythrocyte count, and hemoglobin concentration. It was increased in patients with polycythemia due to pulmonary disease and in patients with increased blood volumes due to congestive failure — *Activity of carbon anhydrase in the blood. Study of patients with dyspnea consequent to chronic cardiac and pulmonary disease, M D Altshule & H D Lewis, Arch Int Med, May 1949, 83 547* — (G C Leiner)

#### PUBLIC HEALTH AND EPIDEMIOLOGY

**Reaction to Vole Tubercle Bacilli** — It has been shown that vole tubercle bacilli are only slightly pathogenic for rabbits and guinea pigs. Injection of caseous material from lesions of naturally infected voles or of living vole tubercle bacilli protects these animals against virulent mammalian tubercle bacilli. Pathogenicity of the vole organism for calves is low, its immunizing power is greater than that of BCG, all injected calves developing strongly positive tuberculin reactions. In the current study, 16 patients with far advanced tuberculosis were injected intradermally with 0.0001 mg of a culture of living vole tubercle bacilli. A marked local reaction developed, consisting of a tiny red papule surrounded by an area of erythema. This slowly increased in size, reaching its maximum in ten days. In most cases, the papule became a pustule. There was no lymphadenopathy or constitutional reaction. The intensity of the reaction paralleled the Mantoux reaction. For injection in other cases, the bacilli were killed by heat, the reaction was slightly less intense but

of the same character. When dosages up to 0.1 mg were used, the same reactions were obtained but the intensity was in proportion to the dosage scale. In no case was a patient affected adversely — *The intracutaneous injection of vole tubercle bacilli in tuberculous persons, C Cameron & I A Purdie, Tubercle, December, 1946, 27 195* — (A G Cohen)

**Vaccination with Vole Bacillus** — Vaccinations were carried out with the murine type of tubercle bacillus (vole bacillus) in 2 communities. A group of 444 persons with a low incidence of tuberculosis was tested, 116 were negative to intradermal tests with 0.1 cc of Old Tuberculin 1:100. Forty-eight of the nonreactors were vaccinated. Only one case of tuberculosis developed in the control group and none appeared in the vaccinated group. After vaccination all of the latter became sensitive to 0.1 cc of OT 1:100. Sensitivity to OT 1:10,000 appeared but gradually waned. In another community with a high incidence of tuberculosis, there were 179 nonreactors among 441 persons tested. Eighty-one of the nonreactors were vaccinated, one case of tuberculosis developed in this group. In the control group, there were 4 deaths and 4 other cases. This difference is statistically significant — *Vaccination with the murine type of tubercle bacillus (vole bacillus), A G Wells, Lancet, July 9, 1949, 1 55* — (A G Cohen)

**Tuberculosis in Belgian Congo** — The control of tuberculosis in the Congo has become more difficult since the war because of the rapid increase in population which has accompanied industrial development. Besides the native villages, many new, larger population centers have developed. There are now over 14,000,000 persons, mostly Negroes, in the Belgian Congo and Ruanda-Urundi. Adequate food and hygiene are more easily provided in the large groups under the direct management of rich and powerful industrial companies which are responsible for the workers' housing, food, education, and medical care. The central government must pro-

vide for other groups. A recent study showed that in certain mining locations 80 per cent of the workers and 64 per cent of their wives gave positive tuberculin reactions, as did 30 per cent of children up to fifteen years of age. Most cases of active tuberculosis were found in adolescents and young adults. Accurate mortality statistics were not available and it is impossible to say to what extent the disease is increasing or the population is gradually becoming immunized. Fulminating cases which soon cease to be centers of infection are less to be feared than the more chronic cases which are now increasing in number. Meningitis is rare, military tuberculosis occurs more often than it is diagnosed. Many cases of ulcerocaseous pulmonary tuberculosis are not diagnosed. Adolescents often die of a primary infection. The author emphasizes the area's need of trained physicians and advocates BCG vaccination of negative reactors exposed to infection.—*Les problemes relatifs a la tuberculose chez les noirs au Congo belge en 1948, J. Firket, Acta Tuberculosea Belgica, February, 1949, 1 3*—(A. T. Laird)

**Tuberculosis in Mental Hospitals**—In 1945 the resident population of the mental hospitals in California was 25,810, forming 0.3 per cent of the state's population and contributing 4.4 per cent of the deaths from tuberculosis. The death rate of 657 per 100,000 in mental hospitals and 361 in institutions for mental defectives compares with a total tuberculosis death rate of 43.4 for California. Contrary to popular belief, there is considerable patient movement in mental institutions. In 1944-1945 there were 8,703 admissions and 3,069 returned from parole or escape. There were 5,397 patients paroled and 2,524 discharged from parole in that year. Thus, any existing reservoir of infection in mental institutions constitutes a potential hazard to the non-tuberculous resident patients and employees and to the population at large. During an eleven month survey begun in 1946, 25,914 chest photoroentgenograms were made of mental patients in 7 hospitals. Of these, 2,139, or 8.25 per cent, were found to have evidence

of pulmonary tuberculosis. This represents previously unsuspected cases, inactive as well as active, but does not include calcified primary lesions, pleural effusions, or pleural thickening. Of 4,832 patients surveyed, 622 had been residents for a maximum of only six months and this prevalence (1.6 per cent) can be considered essentially the prevalence on admission. This is higher than general population surveys but is about the same as that found in general hospital admissions. The prevalence of tuberculosis in the group resident for five years or more was 8.8 per cent, in contrast to 3.0 per cent among those resident less than five years. Prevalence of tuberculosis was higher among patients with dementia praecox, probably because they are hospitalized longer and therefore have greater opportunity for exposure. Fifty-five per cent of the cases discovered were classified as minimal, 36 per cent as moderately advanced and 9 per cent as far advanced. One-seventh of the cases showed evidence of cavitation and another 5 per cent were suspicious. Among the far advanced cases 71 per cent had cavitation. The cavitory cases represent more than one per cent of the total resident population of the hospitals. Of 3,321 employees, 2.7 per cent had evidence of reinfection tuberculosis. In the hospitals showing a higher prevalence among patients, there was also a higher percentage of cases among employees. Conclusions reached were (1) all new admissions must be X-rayed, (2) all resident patients should have films taken, and (3) all patients with communicable tuberculosis should be segregated.—*Tuberculosis control program of nine California mental institutions (results of initial chest X-ray survey), W. R. Oechsl, U. S. Pub. Health Rep., January 7, 1949, 64 4*—(E. A. Rouff)

**Tuberculosis Control**—The U. S. Public Health Service is engaged in the following tuberculosis control activities: (1) Roentgenographic surveys in 92 American cities with populations over 100,000. An attempt is made to obtain a chest roentgenogram of every individual over the age of 15 in each community. Of the lesions which required further study,



80 per cent were unknown before the survey (2) Investigations on BCG as an immunizing agent against tuberculosis The various methods of administering the vaccine are being evaluated Attention is called to the importance of special control measures to be taken in mental hospitals where the mortality from tuberculosis is often 10 times the rate for the general population Surveys of the tuberculosis control activities in the various states reveal a great divergence in the efficacy of the different control programs The U S Public Health Service supplements the activities of the states, where necessary—*Summary of tuberculosis control activities, F J Weber & R J Anderson, Am J Pub Health, April, 1948, 38 512*—(M B Lurie)

**Eradication of Tuberculosis**—The tuberculosis mortality in Minnesota was reduced from 120 per 100,000 in 1911 to 20 in 1947 This was accomplished by (1) isolating infectious cases, (2) tracing the sources of contagion for ill children and adults, (3) eliminating exposure to infected domestic animals, and (4) using roentgenographic surveys In the past 30 years, the mortality in children was reduced by 88 per cent, and in infants by 93 per cent The morbidity from tuberculosis is so reduced that many beds in the state sanatoriums are vacant In the twenties and thirties many student nurses in the medical school developed tuberculosis, this is a rare occurrence at present Furthermore, the attack rate was as high as 100 per cent among the non-reacting nurses, it is now only 5 per cent Thirty-three per cent of beginning medical students reacted to tuberculin in 1928, in 1946 only 6 per cent were positive The rate of positive reactions in grade school children has declined from 47 to 7 per cent in a similar period—*Eradication of tuberculosis by epidemiological methods, J A Myers, Am J Pub Health, April 1948, 38 516*—(M B Lurie)

**Relapse in Pulmonary Tuberculosis**—A five year follow-up study was made of 256

patients whose sputum had contained tubercle bacilli Of these, 73 had been discharged as recovered to return to full work, 52 as quiescent to resume full work, 17 with active disease to do full work, 35 with limited working capacity to have various stages of activity, and 79 others, including those totally incapacitated In the recovered group, 8 cases relapsed In the quiescent group, one-third recovered, another third remained quiescent, and the remainder deteriorated Of the patients with active disease who returned to full work, one-half died Since 10 per cent of "recovered" cases break down within five years, more may relapse later, suggesting that a constant check is necessary In 9 of a group of 14 relapsed cases which were studied closely, there were features of the patients' life situation which were conducive to breakdown A case of tuberculosis must be considered a long-term liability from the viewpoint of working capacity—*Relapse in pulmonary tuberculosis, W Tattersall, Tubercle, April, 1949, 30 74*—(A G Cohen)

**Rehabilitation of Tuberculous Patients**—The author conducts a resettlement clinic for tuberculous outpatients in Wallasey, a borough with a population of about 100,000 A "score card" is made up for each new patient Its components, with the maximum grade for each, are prognostic index 50, respiratory and circulatory index 20, work index 10, and home index 10 This is used only as a guide since each case has to be considered individually A large proportion of persons with pulmonary tuberculosis are capable of working in industry and no single factor determines employability A positive sputum reduces it but is not *per se* disabling After discharge from the sanatorium, the patient attends a sheltered workshop until he graduates into ordinary industry—*Reablement of tuberculous patients, R Grenville-Mathers, Lancet, April 2, 1949, 1 463*—(A G Cohen)

# THE SURGICAL TREATMENT OF RECURRENT AND CHRONIC SPONTANEOUS PNEUMOTHORAX OF NONTUBERCULOUS ORIGIN<sup>1</sup>

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## INTRODUCTION

Spontaneous pneumothorax is a familiar subject to all who are interested in chest disturbances. The frequency with which it occurs in apparently healthy people, and its usually benign course in such instances, is in striking contrast to its appearance in cases of far advanced tuberculosis. In the latter, spontaneous pneumothorax is of serious import and not infrequently is a landmark on the road to death. In this group the underlying disease is of paramount importance. In the nontuberculous cases there is frequently no serious underlying disease.

Spontaneous pneumothorax of nontuberculous origin may be grouped into three simple classes. In the first are those cases in which there is a single attack from which the patient recovers without incident or sequelae. In the second group are those in which there are recurring attacks. These may be of short duration, interfere little with the patient's activities, and require little treatment, or they may require aspiration of the air. In some cases, however, the pneumothorax persists for weeks or months and makes the patient an invalid. These require some form of treatment that will prevent the recurrence of the pneumothorax after re-expansion has been obtained. In the final group are cases in which a pneumothorax develops and the lung fails to re-expand spontaneously or after repeated aspiration of air. For these, the writers believe open operation should be used although many cases have been reported in which re-expansion has followed the induction of a chemical pleuritis.

Since Spengler (6) in 1906 suggested the use of silver nitrate injections to induce a chemical pleuritis to prevent the recurrence of pneumothorax of nontuberculous origin, this and various other agents have been used with considerable success. The underlying pathology in such cases has usually been a localized area of emphysema or scattered emphysematous blebs on the surface of the lung. In 1939, Hennell and Steinberg (4) reported the successful treatment of 5 cases of recurrent and chronic, tense pneumothorax by means of injections of glucose, iodized oil, or one followed by the other. Brock (3) in 1948 reviewed the subject of the treatment of these forms of pneumothorax and reported the largest series of cases in the literature. Among 71 cases of spontaneous pneumothorax of nontuberculous origin, he presented 46 chronic cases and 25 recurrent ones. In 8 of the chronic cases there were large cysts which required excision, or lobectomy. All of the others were treated by the induction of a pleuritis with silver nitrate. The treatment proved successful in all cases.

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In the present communication, 18 cases of spontaneous pneumothorax are presented. In 8 the pneumothorax was recurrent, in 11 it was chronic. Operation was performed in all. Three of the chronic cases had bronchiogenic cysts which had to be excised, or treated by lobectomy. In 6 of the chronic cases it was necessary to do decortications of the lung in order to bring about its expansion. A brief report of these cases will be given and the management of these forms of pneumothorax will be discussed.

*Origin of nontuberculous pneumothorax.* The origin of the usual case of spontaneous pneumothorax not due to tuberculosis is the rupture of a peripheral air sac in the presence of a free pleural space. Such dilated alveoli are known to occur frequently in normal lungs. Their rupture as the result of a sudden increase in intra-alveolar pressure is not remarkable. When this event is not associated with the presence of some inflammatory process in the underlying lung or pleura, there is collapse of the lung and the leak becomes sealed. The ruptured area heals and the lung re-expands. When there is underlying emphysema, or some chronic inflammatory process, the decrease in vital capacity may be severe. However, unless the air is leaking from an involved area, it tends to stop quickly and the lung re-expands. Ruptures of veins in parts of the lung affected by active inflammatory processes will usually result in a pyopneumothorax, or hemopneumothorax which will not be considered in this presentation.

### OBSERVATIONS

The management of cases of recurrent pneumothorax of short duration usually does not involve surgical procedures. Conservative measures usually suffice. These include the injection of various irritating substances, such as silver nitrate, glucose, and iodized oil, after it has been demonstrated that the lung can re-expand.

The cases of recurrent pneumothorax of longer duration can be more certainly cured by open operation, as the underlying cause of the leak can be corrected and provisions made for maintaining the expansion of the lung. Eight of our patients had this type of recurring pneumothorax, and all were subjected to operation. They had pleural poultice with talc and sulfanilamide, had this in combination with resection of the leaking emphysematous blebs, or had simple excision of the blebs.

Chronic pneumothorax means that the lung remains collapsed and shows no tendency to re-expand. There were 11 patients in this group. Although tuberculosis was suspected and searched for in each case, it was not found. In general, the two main causes of the pneumothorax were the persistence of a broncho-pleural leak, and/or the encasement of the collapsed lung in adhesions, or an inelastic membrane which prevented its re-expansion. These factors will be considered in the presentation of the individual cases.

In presenting our cases we shall group them according to the type of pneumothorax and according to the underlying etiological factors. Only the essential features will be given and the illustrations will be limited to examples of the different types of cases. With one exception, all of the cases being reported were seen in army hospitals during the last war. Long follow-up studies have not been

possible in every case, but they are considered to have been of sufficient length to allow for a reasonably satisfactory evaluation of the results. In no instance have we been aware of the recurrence of the pneumothorax after our surgical treatment. There were no deaths and no serious complications.

#### RECURRENT SPONTANEOUS PNEUMOTHORAX

Eight patients who had recurrent, spontaneous pneumothorax were treated by open thoracotomy. In none of them was there evidence of any underlying chronic disease. In 3 instances no cause for the pneumothorax could be found. In the other 5 cases emphysematous blebs were thought to be the source of the pneumothorax.

##### *Etiology Unknown*

Of the patients in whom no etiological factor could be found, the first was 21 years old and had had five recurrences of his pneumothorax within three years. The second also was 21 years old and had had two attacks in one year. The third was 23 years old and had had three attacks in two years. They were operated upon and, after it was determined that the lung could fully re-expand, the entire pleural surface was dusted with talc mixed with 0.3 Gm. to 10 Gm. of sulfanilamide crystals. The chest wall was then closed without drainage. The lungs remained expanded and there was no need for thoracentesis. They were followed for periods of ten, twelve, and seventeen months without signs of recurrence.

##### *Emphysematous Bleb*

In the next group of patients a single emphysematous bleb was considered to be the etiological agent in one, and in the other there were four blebs (figures 1 and 2). The first patient was 26 years old and had had three attacks of pneumothorax between November 1942 and May 1943. The second was 29 years old and had had four attacks between January 1943 and December 1944. In both cases the blebs were excised and the defects sutured. After complete re-expansion of the lung, the chest wall was closed in layers without drainage. In neither case was aspiration of the chest necessary after the operation. No long time follow-up was possible in either case, but it was extremely unlikely that there was a recurrence as the men were still in the army and would have been referred back to one of us if there had been any further trouble.

In the final group of cases of recurrent pneumothorax, the lungs were found to have so many blebs on their surfaces that removal of them was not attempted. Instead, the pleural surfaces were dusted with talc and sulfanilamide after it had been demonstrated that the lungs could be fully expanded and the chest wall closed without drainage. The first patient in this group was a 51-year-old woman who had had three recurrences in fourteen months. Her left upper lobe was found to be covered with small blister-like blebs. She needed no thoracentesis after operation and was followed for eight months without evidence of recurrence. The second patient was a 27-year-old man who had had four attacks

of pneumothorax in eight months. His left upper lobe was found to be partly covered with small blebs. Following his operation, his pleural cavity had to be aspirated once. He returned to military duty and had no recurrence during the twenty months he was followed. The third patient was a 31-year-old physician who had had two attacks in two years. He was operated upon a month after the onset of his second attack and while a small pocket of pneumothorax persisted. His right upper lobe was found to be partly covered with small blister-like blebs and a fistula was seen which was thought to be the site of leakage of the air and to have been due to a rupture of one of the emphysematous blebs. The fistula was closed by suture and the lung found to be completely expandable.



FIG 1 (Left) Roentgenogram of chest of patient with recurrent pneumothorax showing marked collapse of the right middle and lower lobes

FIG 2 (Right) Photographs of blebs excised from the surfaces of the right middle and lower lobes of the patient whose roentgenogram is shown in figure 1

The upper lobe was then "iced" with talc and sulfamilamide and the chest wall closed without drainage. No postoperative thoracentesis was necessary. Although no follow-up was obtained in his case, he was a physician and had been instructed to contact one of us should he have further trouble.

These cases were all recurrent in type, and before operation it was known that the lung could fully re-expand or had fully done so. The problem was to ensure the maintenance of this fully expanded position. By applying irritants to the surface of the lung, an inflammatory reaction was started that resulted in thickening of the visceral pleura to such an extent that further rupture of peripheral blebs could not take place. The possibility that the recurrence of the pneumothorax was prevented by the production of a pleural symphysis must also be considered. Certainly the pleural reaction must produce a temporary symphysis, but that this may not be permanent is seen in many cases of empyema in which,

even after surgical drainage, full restoration to normal seems to occur. Also cases of pneumothorax have developed after apparent recovery from an empyema. Hennell and Steinberg (4) report a case in which, following the disappearance of fluid from the chest of a patient with a drained, postpneumonic pyopneumothorax, the pneumothorax persisted until a chemical pleuritis was created by the injection of iodized oil. This case would seem to indicate that the closure of the bronchopleural fistula by the chemically induced pleuritis was more important than the normal tendency to pleural symphysis as the result of the pre-existing empyema.

#### CHRONIC SPONTANEOUS PNEUMOTHORAX

The cases of true, chronic spontaneous pneumothorax, in which it was impossible to bring about re-expansion of the lung before operation, numbered eleven and can be conveniently divided into two main groups. In the one were those in which a definite source for the pneumothorax could be found and, in the other, those in which it was impossible to determine its origin.

##### *Source of Pneumothorax Known*

The cases for which a definite source of the pneumothorax could be found included 3 in which there was a leaking bronchogenic cyst, one with a leaking emphysematous cyst, one in which a band adhesion apparently maintained the patency of a bronchopleural fistula, and 4 in which small leaks in the surface of the lung could be detected.

*Rupture of pulmonary cyst.* The cases in which the cause of the pneumothorax was most obvious were those in which there had been a rupture of a pulmonary cyst. In 3 the cysts were bronchogenic, and in one they were emphysematous. In the bronchogenic ones the problem was merely that of removing the cyst. In 2 it was possible to do so without sacrifice of lung tissue, but in one it was necessary to do a lobectomy. In none of these were there any adhesions which interfered with the re-expansion of the lung. In the case of the emphysematous cysts the chief obstacle to re-expansion of the lung was its encasement by binding adhesions.

The first of the group, chronologically, was a 31-year-old man who had had a pneumothorax for six months before operation. In addition to dyspnea, he had had hemoptysis, cough productive of pus, fever, and chills for the first six weeks. At operation the left upper lobe was found to be largely replaced by a cyst which had ruptured and from which air had escaped. The upper part of the lower lobe was studded with small cysts. The upper lobe was resected and closed drainage of the chest established. His lung promptly expanded to fill his chest but roentgenograms showed evidence of a cyst in his opposite lung, which had not been apparent before operation. Pyelographic studies revealed apparently incomplete rotation of his kidneys and bizzare deformities of the pelvis and calyces. The study of the resected lobe and these other findings would place this case in the group of true congenital cystic disease of the lungs. He was examined nineteen months after the operation and found to have no evidence of further

chest disease. A year later he still had no evidence of recurrence of his pneumothorax.

The next 2 patients with bronchogenic cysts were diagnostic problems, but then management was simple. The first was 46 years old and his symptoms were all gastrointestinal, the pneumothorax had persisted for four months before his operation. Closed thoracoscopy showed a large cyst collapsed against the surface of the deflated right lung. At operation one month later, the cyst was found to be intact and occupying the entire pleural cavity. It arose from the upper lobe near the origin of the bronchus to this lobe. Its walls contained islands of cartilage and the lung around the base of the cyst felt as if it contained an abnormal amount of cartilage. The cyst was excised with a minute amount of lung tissue and the chest wall was closed without drainage after the lung had been fully expanded. No postoperative aspiration of the chest was necessary, and the lung remained expanded up to the time he was last seen, two months after the operation.

The third of the patients with bronchogenic cysts had symptoms suggesting coronary arterial disease. He was 40 years old and his first attack of severe substernal pain, with radiation to the left arm, was relieved by nitroglycerine. No roentgenogram of the chest was taken at the time, but an electrocardiogram was made which showed no abnormality and he was returned to duty. This was in March 1944. Another attack occurred in seven months and again the electrocardiogram was normal, but this time a roentgenogram of the chest was made which showed evidence of a cyst, or a localized pneumothorax. Two months later at Kennedy General Hospital, studies showed no evidence of heart disease but the roentgenogram showed a pneumothorax in the right upper chest. Closed thoracoscopy revealed a pneumothorax and a partly collapsed cyst arising from the right upper lobe. Four days later the cyst was resected by cutting across a base of normal-looking lung tissue. The middle lobe was seen to have a smaller lobe projecting from its lower anterior surface, and the lower lobe was almost completely divided into two. One of the lower lobes was retrocardiac in position. There was no evidence of anthracosis in this lung in spite of the fact that the patient had lived in cities most of his life. His convalescence was uneventful, and three months later his lung was still fully expanded and he had had no more symptoms of any kind.

The final patient in this series was a 55-year-old Russian plumber. In the evening, following a strenuous afternoon in which he had lifted a heavy boiler, he suddenly became short of breath. Not until ten days later was the cause for his dyspnea found when a roentgenogram of his chest showed an extensive pneumothorax. Repeated aspiration of the air only gave temporary relief and he had continued as a chronic invalid. He was first seen by one of us five months later. He was found to have an extensive pneumothorax (figure 3). Before operating on him it was decided to try the effect of continuous decompression. This only resulted in his developing an extensive interstitial emphysema as the air under pressure escaped along the tract of the needle. Apparently, the fixation of his mediastinum and the presence of adhesions binding his lung to a part of the chest wall saved him from the usual effects of a tension pneumothorax.

When he was operated on six days later the lung was collapsed except for extensive attachments of the upper lobe to the lateral chest wall. There were a

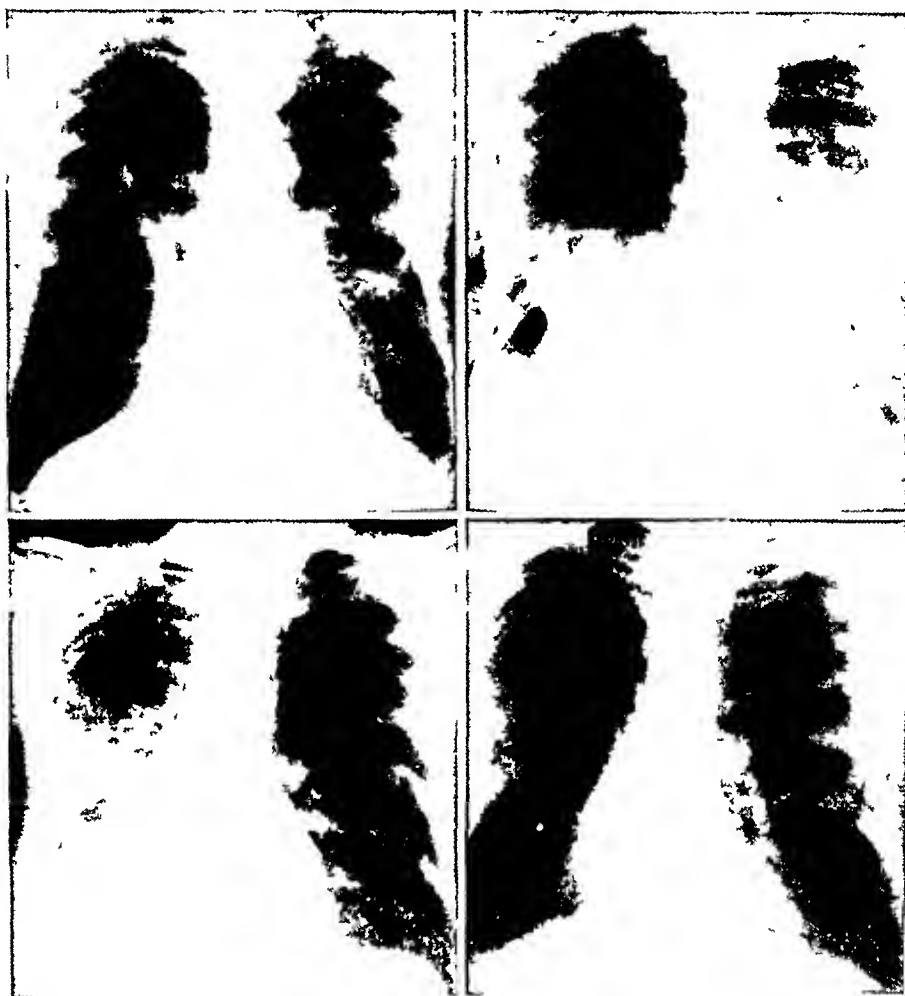


FIG 3 (Upper left) Roentgenogram of chest of patient with chronic pneumothorax due to rupture of a large emphysematous cyst. Adhesions prevent the complete collapse of the upper lobe.

FIG 4 (Upper right) Roentgenogram of the chest of the same patient the first morning after the operation showing the lung symmetrically collapsed and marked interstitial emphysema.

FIG 5 (Lower left) Roentgenogram of the same chest five days after operation, showing complete re-expansion of the right lung and a small amount of interstitial emphysema.

FIG 6 (Lower right) Roentgenogram of the chest of the same patient eighteen months after his operation. No abnormalities are noted except for the rib defect produced by the operation.

number of large cysts buried in the lung and all was found to be escaping from the largest one. The opening was not obvious. Although the only way in which the cysts could be eradicated was by total pneumonectomy, this was not possible.



as there were thought to be large cysts in the opposite lung. Accordingly, the lung was decorticated and the cystic areas infolded into the normal appearing lung surrounding them. Attempts to suture the area from which the air was thought to be escaping were futile but the area was infolded as were the cysts. Following these procedures the lung could be expanded without interference, but full expansion was not attempted because of the danger of tearing the sutured areas. Closed drainage was established with a single tube which was connected with a water trap.

Four hours after the operation he had developed extensive interstitial emphysema which was progressive and only came under control after another drainage tube had been inserted into his pleural cavity (figure 4). From then on he rapidly recovered, and at the end of five days the lung was fully expanded (figure 5) and has remained so ever since. A roentgenogram of his chest eighteen months after the operation (figure 6) shows the present appearance of his chest. This case emphasized the need for decortication in such cases of chronic pneumothorax, and more especially showed the need for really adequate closed drainage when the source of a tension pneumothorax cannot be definitely eradicated.

Among the other cases in which it was thought that a definite source for the pneumothorax could be demonstrated, the first was a 37-year-old man who had had three attacks of pneumothorax during a period of six months and whose lung had shown no tendency to re-expand following the last episode. Roentgenograms of his chest showed an extensive pneumothorax on the right with a band adhesion running from the upper part of this lung to the chest wall. On thoracoscopy the adhesion was seen to be arising from a rather normal-looking area of lung and no evidence of a fistula could be found. The adhesion was divided and the lung collapsed symmetrically. Gradual re-expansion of the lung occurred and the patient was discharged with a normal-appearing chest roentgenogram. No follow-up observations have been obtained in this case although he was operated upon in November 1943. The persistence of the pneumothorax in this patient was thought to be due to the rupture of a peripheral bleb and the maintenance of the patency of the opening by the attachment of the adhesion to the edge of the defect. Although no fistula could actually be seen, the sequence of events would tend to support the hypothesis advanced. In cases of tuberculosis, tension pneumothorax has been successfully treated in this manner in a number of cases.

*Peripheral fistula or bleb.* There were 4 cases in which the persistent pneumothorax was found to be due to definite leak of air from a peripheral fistula or from a peripheral bleb. In each it was possible to close the defect by suture and to bring about re-expansion of the lung. The first of these was a 25-year-old man who was discovered to have a pneumothorax in June 1942. He was carefully studied in two hospitals and efforts were made without success to cause re-expansion of his lung. He was finally operated upon in December 1943. A small bleb was found on the extreme apex of the right upper lobe from which air could be seen to escape when this area was covered with normal salt solution. The area was incised with catgut sutures and further covered with a piece of

muscle which was held in place by "tissue glue" (Sano (5)) made from a suspension of the patient's red blood cells and plasma. This "tissue glue" was also applied to the entire surface of the upper lobe and the adjacent parietal pleura. The pleura elsewhere was vigorously rubbed with dry gauze to produce a pleuritis. The lung was inflated and the chest wall closed without drainage. Small amounts of fluid had to be aspirated from the pleural cavity on two occasions, and the lung gradually completely re-expanded. He was returned to active duty in the army and fourteen months later reported that he was in excellent health and had had no further attack of pneumothorax.

The next patient in this group was 34 years old. He had had his pneumothorax for five months and, after all attempts to bring about re-expansion had failed, he was operated upon. His lung was found to be completely collapsed and the air under positive pressure. A bleb was found in the depth of an incomplete fissure between the left upper and lower lobes and air was seen to be escaping from it. This area was buried by means of catgut sutures and further covered with muscle and pleural grafts. Other blebs were seen on the surface of the lung but none allowed the escape of air. The lung could not be inflated because of the presence of an inelastic membrane which covered the posterior and medial aspects of the lung. This was incised and peeled off the lung, allowing it to re-expand. Closed drainage of the pleural cavity was established and the chest wall closed. Re-expansion of the lung promptly occurred, and he was returned to duty. He was followed for six months without evidence of recurrence.

The third member of this group was a young man who had had a pneumothorax of varying extent for more than a year before being admitted to Kennedy General Hospital in June 1944. All attempts to re-expand the lung having failed, he was operated upon and the lung found to be adherent posteriorly. A definite, small opening was found in the midst of a roughened area on the anterolateral aspect of the left lower lobe from which air was escaping. This area was closed with interrupted sutures of fine silk and re-enforced with two muscle grafts. The lower lobe was prevented from re-expansion by the thick membrane which covered its lower part. This was removed without difficulty allowing the lobe to be fully inflated. Some oozing had persisted from the area in which the fistula had been sutured in spite of the sutures and muscle grafts. Accordingly, a single piece of oxidized gauze (Oxycel) was placed over this area and the oozing promptly stopped. After establishing closed drainage, the chest wall was closed in layers. The lung was slow in re-expanding and required active suction drainage and aspiration of air from the upper part of the pleural cavity before complete re-expansion was established after two months. He was discharged from the hospital in November 1944. A roentgenogram of the chest in September 1946 showed no abnormalities and he was seen in March 1947 after having had no further recurrence of his pneumothorax.

The last in this particular group was a 35-year old man admitted to Kennedy General Hospital with a spontaneous pneumothorax of four months' duration (figure 7). Repeated aspiration had failed to have any effect on the pneumothorax. An exploratory thoracoscopy showed the lung to be nonexpansile

but no fistula could be seen. Three weeks later he was operated upon and the lung was found to be encased in an inelastic membrane (figure 8) and near the

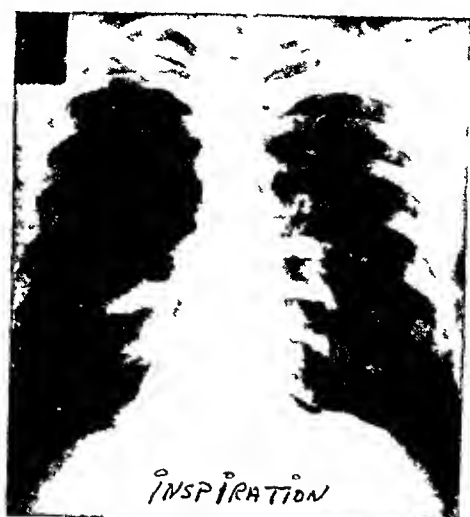


FIG 7 (Top) Roentgenogram of the chest of a patient with chronic pneumothorax due to a ruptured emphysematous bleb

FIG 8 (Lower left) Photograph of the lung at operation showing the lower part of the lung encased in an inelastic membrane which prevented its expansion

FIG 9 (Lower right) Photograph of the lung at operation showing the bleb from which air was escaping

apex of the upper lobe was in emphysematous bleb that ballooned out when the intrabronchial pressure was raised (figure 9). Although no air was seen to escape from this bleb, it was thought that it probably was the source of the pneumothorax and this area was buried in the lung parenchyma by means of

interrupted sutures of fine silk. Because of its encasing membrane the lung could not be expanded until a decortication had been done. This was accomplished by actual removal of the membrane in large pieces and by incising the membrane in other areas and causing it to split further by active expansion of the underlying lung. Complete re-expansion was obtained. Closed drainage was used and the lung rapidly filled the pleural space and remained expanded. Two years later he had a spontaneous pneumothorax in the opposite chest from which he promptly recovered.

These 4 cases all showed evidence of the source of their pneumothorax, and in 3 the lung could not be expanded until after a decortication had been done. In each of these cases the chief barrier to spontaneous re-expansion was the presence of the inflammatory capsule, or of an adhesion.

#### *Source of Pneumothorax Unknown*

The other main division of our cases of chronic pneumothorax was made up of 2 in which no source for the pneumothorax could be found, but in each of which the lung was prevented from re-expanding by binding adhesions or a covering membrane. The first was a 23-year-old man who had had an acute upper respiratory infection followed by pleurisy with effusion. The effusion cleared but he was left with a chronic pneumothorax. Seven months later he was admitted to Kennedy General Hospital. After exhaustive studies to determine the etiological factor had proved fruitless and repeated aspiration of air had had no effect on the pneumothorax, he was operated upon, thirteen months after the onset of his illness. At operation no source for the pneumothorax could be found, but there were dense adhesions binding the lower lobe to the diaphragm and paravertebral region. After dividing these adhesions, the lung could be fully expanded. Closed drainage was established and the chest wall closed in layers. Drainage had to be maintained for two weeks before the lung fully expanded. Because of the symptoms of a psychoneurosis, he was kept under observation for four months before discharge and there was no recurrence of the pneumothorax during this time. Attempts to follow him have been unsuccessful. It is believed that the pneumothorax developed during the period of the acute pneumonitis, that the effusion added to the collapse of the lung, and that the associated pleuritis fixed the lung and prevented its re-expansion after the active infection had subsided. The fluid was absorbed but the air remained.

The other patient in this small group also was 23 years old but he had never had any illness prior to the discovery of his pneumothorax. This discovery took place overseas and he was returned to this country when the lung failed to re-expand. Attempts to bring about re-expansion by repeated aspiration of the air proved ineffectual and he was operated upon five months after the onset of the pneumothorax. At the operation no evidence of a fistula could be found or of any area from which it seemed air might have escaped. The lung was encased in an elastic membrane (figure 10). Decortication was easily done and the lung completely reinflated (figures 11 and 12). Closed drainage was used for a short time and the lung promptly re-expanded and remained so. One ven liter

he wrote that he had been working for some months and had had no further trouble

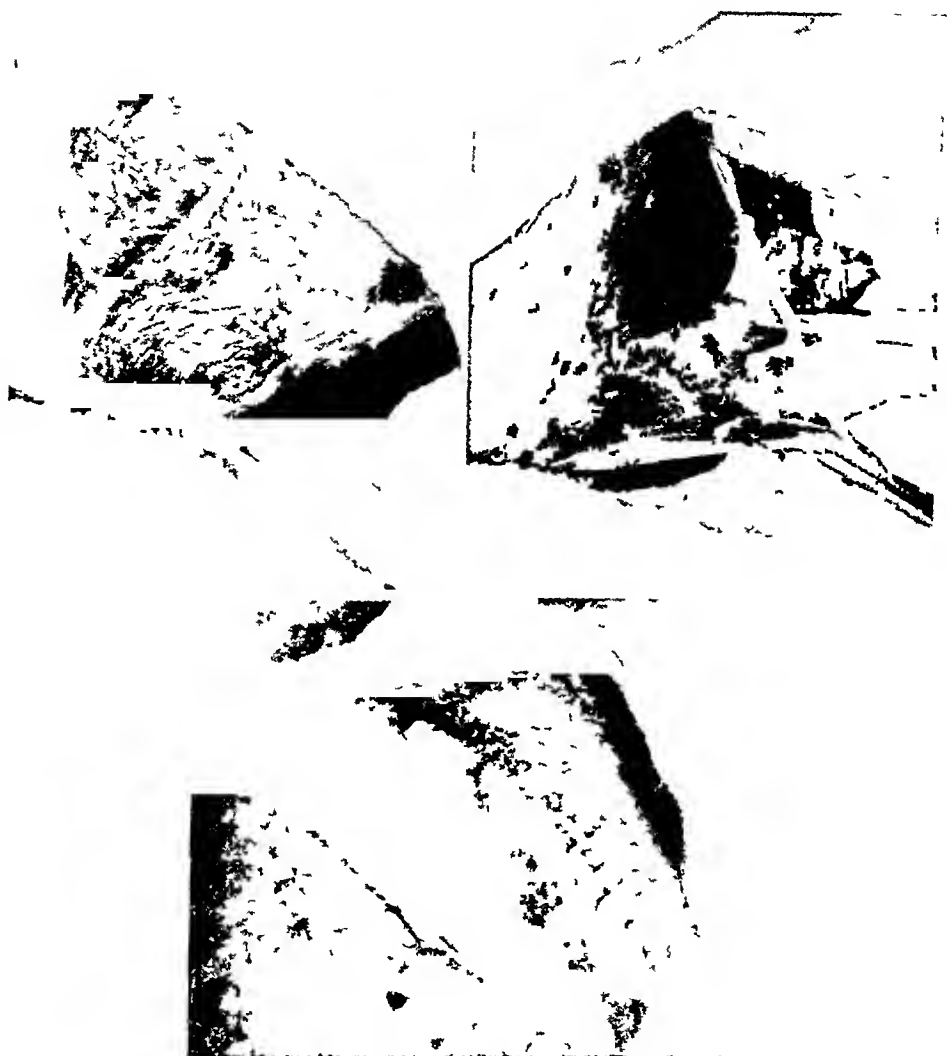


FIG 10 (Upper left) Photograph of the lung at operation of patient with pneumothorax showing the collapsed lung encased in a membrane

FIG 11 (Upper right) Photograph at operation showing the membrane being stripped from the surface of the lung

FIG 12 (Bottom) Appearance of the lung after the decortication showing its normal markings

### DISCUSSION

In the cases of recurrent pneumothorax in the present report, it seems apparent that the etiological factor was the rupture of a peripheral bleb. Following this rupture and the establishment of a pneumothorax, the lung collapsed and

the site of air leakage became sealed. Re-expansion then occurred. The ensuing pleural reaction was not sufficiently great to prevent rupture of other blebs, however, or to produce symphysis of the pleural leaves and, when the intra-alveolar pressure again became suddenly increased, the same bleb or another ruptured and pneumothorax again appeared. The problem of the management of these cases was that of preventing further leaks from the lung and maintenance of the lung in its fully expanded state. It cannot be denied that good results in certain cases have been achieved by the induction of a chemical pleuritis with silver nitrate, iodized oil, concentrated glucose solution, and by closed pleural poudrage with talc. Nevertheless, it has been our belief that in cases of recurring pneumothorax of long standing, the open operative approach offers more certain success. Such an approach allows for the direct study of the involved lung and definitive management of the presenting lesion. Although a wide range of vision may be afforded through the use of the thoracoscope, the exploration can never be as complete as when the chest is widely opened.

Among the 11 cases of chronic pneumothorax, the site of leakage of air was apparent in 9 of them. The rupture of large bronchiogenic or emphysematous cysts occurring in 4 of the 9 cases was an obvious cause for the pneumothorax, and the size of the bronchial communication easily accounted for the chronicity. At the same time, however, the size of the fistula should have allowed for infection of the pleural space of sufficient degree to produce an effusion. In none of the 3 cases with bronchiogenic cysts was this true. In the case with emphysematous cysts there had been a pleural reaction of sufficient degree to produce binding adhesions, although at no time was there evidence of an effusion. These adhesions would have been sufficient in themselves to prevent the lung from re-expanding even had the leakage of air stopped. In 4 other patients air could be seen to escape from the lung surface, either from an emphysematous bleb or from an area of localized induration in the lung. In the patient who had had a band adhesion divided by the closed method, no definite fistula was demonstrated, but the progress of the case and its similarity to certain cases of tension pneumothorax occurring in patients with tuberculosis make it seem most likely that a fistula had been held open by the adhesion. Healing of the fistula occurred after the lung had been allowed to completely relax, and the pleural reaction produced by the operative procedure caused the lung to adhere to the parietal pleura and should ensure against a recurrence of the pneumothorax.

In the cases of chronic pneumothorax in which no definite site of leakage could be found, it must be assumed that during the time when the air was leaking from the lung an inflammatory process was in progress which caused the formation of adhesions which later prevented the lung from re-expanding. The first of these patients had a definite pleural effusion before there was evidence of his pneumothorax. He was treated with sulfonamides during this time and they undoubtedly played an important role in sterilizing the pleural cavity. The other patient had had no evidence of pleural infection at any time and had received no sulfonamides or penicillin.

Aside from the persistence of a bronchopleural fistula, the other important

factor in the pathogenesis of these cases of chronic pneumothorax was the trapping of the collapsed lung by adhesions or its encasement in an inelastic membrane. In 6 of the 11 cases it was necessary to do a decortication before the lung could be made to expand, even when the intrabronchial pressure was raised to a high level. This experience is apparently unique if one is to judge from the literature. Except for Brewer, Dolley, and Evans (2), who reported their experience with 15 cases of chronic, spontaneous pneumothorax at the meeting of the American Association for Thoracic Surgery on March 30, 1949, no other authors have noted the importance of decortication in the treatment of chronic pneumothorax. Brock (3), in his recent excellent article, was able to obtain re-expansion of the lung in each of his 46 cases without the use of decortication. Furthermore, except in 8 cases associated with pulmonary cysts which required excision of the cyst or lobectomy, he simply induced a pleuritis by means of the injection of silver nitrate. Also, Alexander and Haight (1), in the paper they presented before the American Trudeau Society in 1947, cited no case in which it was necessary to do a decortication, although open thoracotomy was done in all of their cases. Why the present writers found 6 cases in 11 who needed decortication to allow for re-expansion of the lungs and Brock (3) found none in a much larger series is hard to understand. Perhaps as our series grows in size, the incidence of incapacitating adhesions will decrease. Certainly the recognition of this condition cannot be certain without open thoracotomy and hence this approach is regarded as preferable.

The object of all therapy is to return the patient to a state of health as safely and as quickly as possible. Conditions in individual cases must always determine the line of treatment. It is also important to realize that radical surgery may at times be more conservative treatment than nonoperative management. In the series of cases of chronic pneumothorax reported by Hennell and Steinberg (4), in which intrapleural injections of glucose or of iodized oil, or of one followed by the other, were employed, the convalescence required from one to six months. In the larger series reported by Brock (3) the duration of convalescence was shorter but the patients had to have repeated chest aspirations, and at times the chemical pleuritis had to be reinduced by further injection of silver nitrate. The longest period of convalescence in any of our cases was two months and most of them were well within two weeks. There has been no recurrence in any of the reported cases, or in our series, and no serious complications.

#### SUMMARY

1 Eight cases of recurrent spontaneous pneumothorax, and 11 cases of chronic spontaneous pneumothorax of nontuberculous origin, are reported. All were cured by operative intervention.

2 The recurrent pneumothoraces were found to be due to the rupture of peripheral, emphysematous blebs in 5 instances. No cause for the pneumothorax was found in 3 patients.

3 In 2 recurrent cases the blebs were excised. In one, with multiple blebs, a fistula was closed and the pleural surfaces covered with talc and sulfanilamide.

In the remaining 5, 2 had multiple blebs and 3 had none, the pleural surfaces were coated with talc and sulfanilamide

4 The etiological factors in the cases of chronic pneumothorax were ruptured bronchiogenic cysts in 3, ruptured emphysematous cysts in one, maintenance of a bronchopleural fistula by the attachment of an adhesion to its edge in one, leakage from emphysematous blebs in 4, and no cause for the pneumothorax could be found in 2 instances

5 The bronchiogenic cysts were treated by excision of the cysts in 2 cases and by lobectomy in one

6 The emphysematous cysts were invaginated and the lung decorticated

7 The adhesion holding open the fistula was divided by the closed method

8 The cases in which a definite leak could be found were treated by suture of the involved area, and in 3 a decortication of the lung was also done in order that the lung might re-expand

9 The 2 cases in which no cause for the pneumothorax could be found required decortication before the lung could be re-expanded

#### CONCLUSIONS

The writers believe that open thoracotomy should be done on all patients with recurrent spontaneous pneumothorax of nontuberculous origin if there is not prompt response to simple aspiration of the air or to the induction of a chemical pleuritis. In all cases of chronic spontaneous pneumothorax of nontuberculous origin, it is believed that operation should be done by the closed method only for the division of isolated adhesions and by open thoracotomy. The open operation makes it possible to deal with the etiological factor and to perform a decortication in those cases in which it is needed. It is believed that binding adhesions play an important role in the chronicity of some cases.

#### SUMARIO

##### *La Asistencia Quirúrgica del Neumotórax Espontáneo Recurrente y Crónico de Origen no Tuberculosos*

1 Los casos comunicados de neumotórax espontáneo de origen no tuberculoso comprenden 8 de la forma recurrente y 11 de la crónica. Todos curaron con la intervención cruenta.

2 Los casos recurrentes resultaron ser debidos a la rotura de flictenas enfisematosas, periféricas, 5 veces, sin que se descubriera la causa en el resto.

3 En 2 casos recurrentes se excindieron las flictenas. En uno, con flictenas múltiples, se cerró una fístula y se recubrieron las superficies pleurales con talco y sulfanilamida. De los otros 5, 2 tenían flictenas múltiples y 3 no tenían flictenas, recubriéndose también las superficies pleurales con talco y sulfanilamida.

4 En los casos de neumotórax crónico, los factores etiológicos fueron quistes bronquiógenos roturados en 3, quistes enfisematosos roturados en uno, mantenimiento de una fístula broncopleurale por la unión de una adherencia a su borde en uno, escurrimiento de flictenas enfisematosas en 4, sin que pudiera descubrirse la causa en 2.



5 Los quistes bronquiógenos fueron tratados por excisión del quiste en 2 y por la lobectomía en uno

6 Los quistes enfisematosos fueron invaginados, decorticándose el pulmón

7 La adherencia que mantenía la fístula abierta fué despegada por el método cerrado

8 Los casos en que pudo localizarse un escurrimiento bien definido fueron tratados por sutura de la zona afectada, y en 3 se practicó además una decorticación del pulmón, a fin de que éste pudiera reexpandirse

9 Los 2 casos en que no pudo descubrirse la causa del neumotorax exigieron la decorticación para que el pulmón pudiera reexpandirse

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# THE SURGICAL IMPORTANCE OF THE ANATOMICAL DISTRIBUTION OF THE PULMONARY SEGMENTS<sup>1,2</sup>

EDWARD M. KENT

(Received for publication May 5, 1949)

An anatomical understanding of, and a universally accepted nomenclature for, the segments of the lungs are undoubtedly of little interest and importance to the members of the medical profession as a whole. Certainly these subjects have no interest to the lay public whatsoever, nevertheless, those of us present today have a vital interest in both. With the rapid advances which have occurred in the medical and surgical treatment of diseases of the lungs, there has been a correspondingly keen curiosity concerning the detailed anatomy of these structures. For the most part, those who have been bitten by this bug of curiosity, this desire to understand more fully the anatomy of the lungs, have come from the fields of anatomy, broncho-esophagology, phthisiology, radiology, thoracic surgery, and from those interested in any type of disease of the lungs. All have contributed in full measure to the advancement of our knowledge in this sphere.

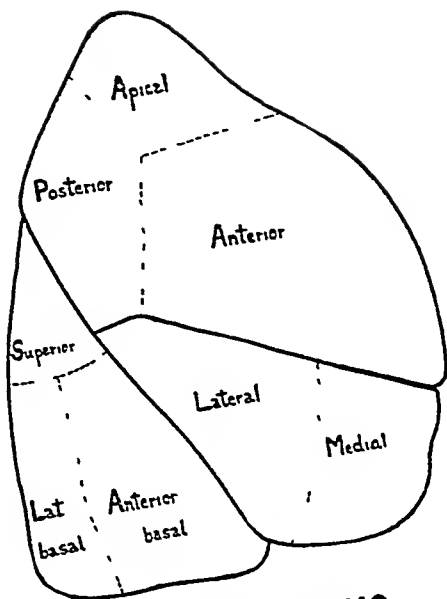
The actual anatomical factors have proved to be universally consistent by the very nature of things, and accordingly, all investigators have agreed rather completely on the distribution of the segments of the lungs. Naturally, as anatomical research continues, we are confronted with an increasing number of anomalies or diversions from the pattern which we have come to accept as normal. Tremendous contributions have been made in our knowledge of the normal and atypical anatomy of the bronchopulmonary segments by Boyden and his co-workers (1, 2), Brock (3), Churchill and Belsey (4), Foster-Carter (5), Jackson and Huber (6), Scannell (7, 8, 9) and many others.

The matter of arriving at a universally accepted nomenclature for the bronchopulmonary segments has met with many obstacles. There have been numerous classifications offered, some overlapping the others in part, but a few have been quite different and distinctive in terminology. Of course, all have represented the best thoughts on the subject by their various originators. Time simply does not permit a review of the many differing systems of nomenclature in this communication.

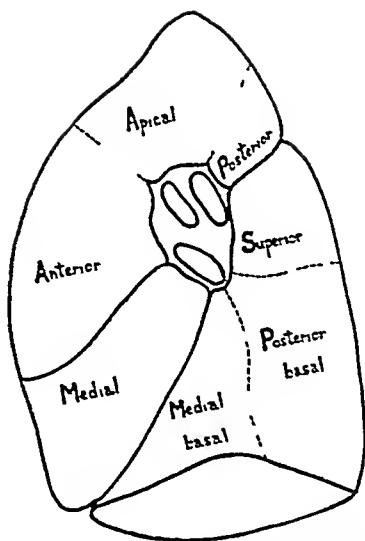
A revised edition of the Diagnostic Standards is in press at this time. When this revision was undertaken, the editors placed the responsibility for the selection of one of the many classifications of the bronchopulmonary segments upon the membership of the American Association for Thoracic Surgery. The choice of this Association has been adopted for inclusion in the revised edition of

<sup>1</sup> From the Department of Surgery, Section of Thoracic Surgery, The University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania.

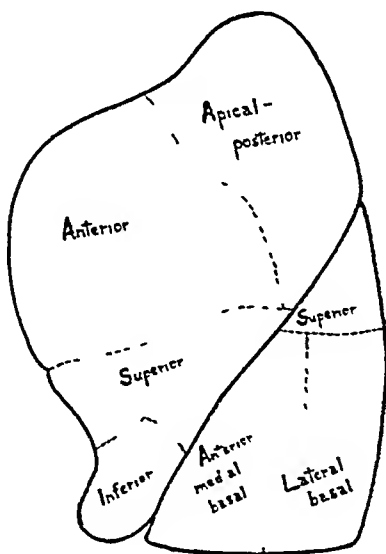
<sup>2</sup> Presented before the Medical Section, as part of the symposium on *Segmental Bronchopulmonary Anatomy*, at the 45th annual meeting of the National Tuberculosis Association, Detroit, Michigan, May 5, 1949.



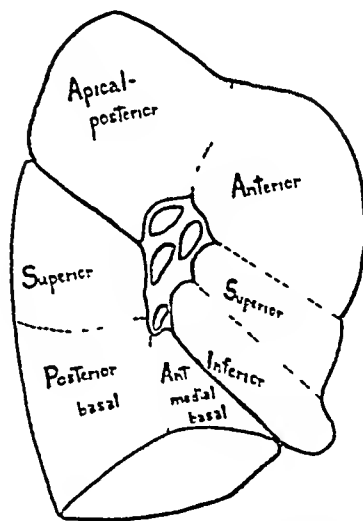
**RIGHT LUNG**



**RIGHT LUNG**



**LEFT LUNG**



**LEFT LUNG**

Fig 1 (Upper left) Jackson-Huber classification Lateral view of diagram of broncho-pulmonary segments of the right lung  
 Fig 2 (Upper right) Jackson-Huber classification Medial view of diagram of broncho-pulmonary segments of the right lung  
 Fig 3 (Lower right) Jackson-Huber classification Lateral view of diagram of broncho-pulmonary segments of the left lung  
 Fig 4 (Lower left) Jackson-Huber classification Medial view of diagram of broncho-pulmonary segments of the left lung

**Diagnostic Standards.** This considered action of the editors has been sincerely appreciated by the members of the Association for Thoracic Surgery. As a result, careful consideration of the entire matter has been undertaken first by a specially

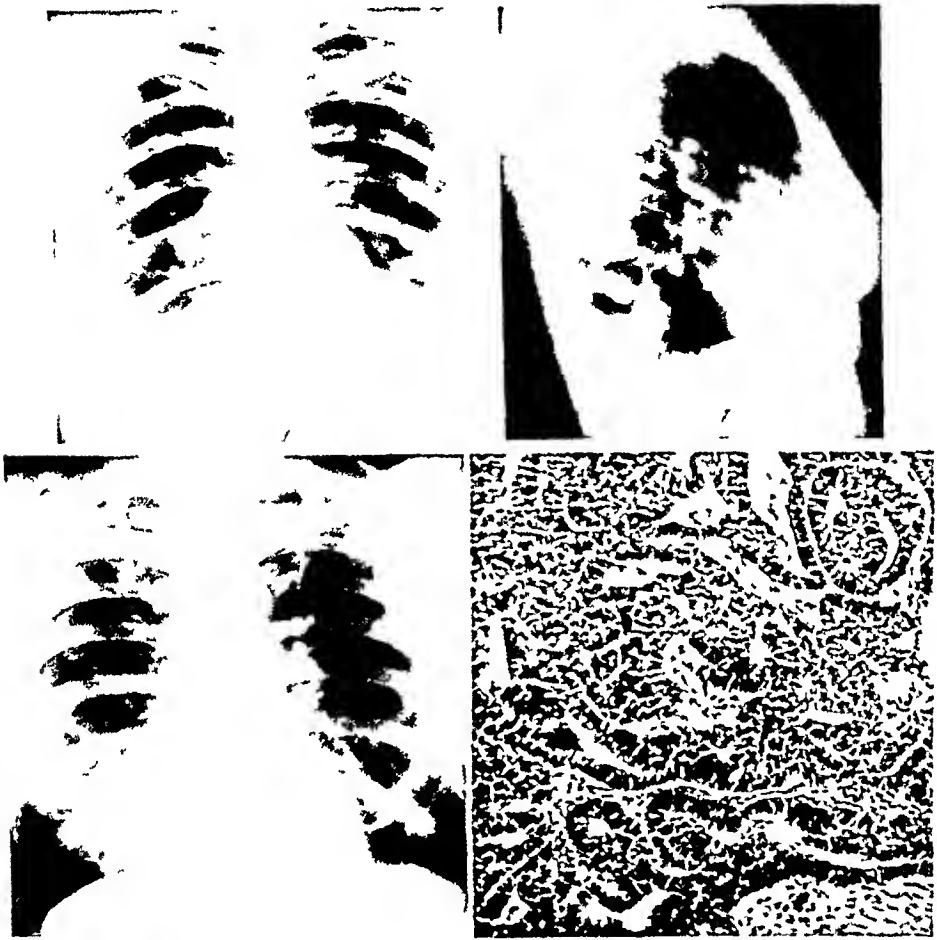


FIG. 5 Solitary pulmonary cyst of right lung (A) (Upper left) PA view (B) (Upper right) Lateral view showing position in superior segment of right lower lobe. A segmental resection of this unit was employed to remove the cyst.

FIG. 6 (A) (Lower left) Solitary round lesion in apical segment of right lower lobe. Patient is a 27-year old male. (B) (Lower right) Segmental resection of superior segment of right lower lobe removed lesion in toto. Frozen section revealed lesion to be papillary adenocarcinoma of metastatic origin. Accordingly, no further resection was performed. Had the lesion proved to be primary pulmonary malignancy, total pneumonectomy would have been performed at this operation. (Note: A primary site has not yet been found.)

appointed committee, and finally by the membership of the Association at the annual meeting in New Orleans in March of this year. The unanimous vote of the Association approved and adopted the Jackson-Huber (6) system of terminology.

In figures 1, 2, 3, and 4 may be seen illustrations of the Jackson-Huber classification. The merits of this nomenclature include consistency, brevity, clarity,

and wide acceptance in this country. Since the necessity of a universally accepted and understood single classification of the bronchopulmonary segments is conceded on all sides, it is fervently to be hoped that universal approval and adoption of the Jackson-Huber nomenclature will follow on this continent, and preferably, in the entire world. We must talk the same language in order that we may understand each other immediately and without the necessity of maintaining in our minds the terminology of numerous, differing classifications.

The surgical application of this knowledge has progressed apace. This has been elaborated upon by Blades (10), Overholt and Lange (11), and by many other contributors. At the present time, the limitations and the over-all scope of this surgical technique have not been explored with finality. All admit that it is of great importance in the surgical treatment of extensive, bilateral bronchiectasis.

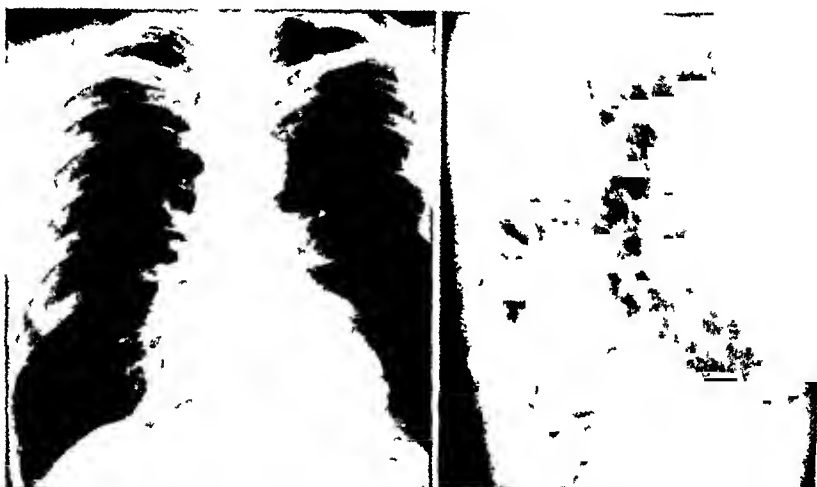


FIG. 7. Solitary tuberculoma of lower lobe of left lung. Resection of superior segment of left lower lobe of lung resulted in complete extirpation of the lesion. (A) (Left) PA view. (B) (Right) Lateral view.

In these patients, it is important that all normal pulmonary tissue be preserved, if possible. It has been pointed out that many such patients have superior segments of the lower lobes which are free of disease while all or some of the basal segments are involved in the disease process. In a much smaller percentage of patients, the basal segments are free of disease but the superior segments show bronchiectasis. Under such circumstances, the principles of segmental resection become of great importance and today they are widely practiced. Boiled down to a few words, these principles dictate the preservation of normal bronchopulmonary segments where possible in such instances of extensive, bilateral bronchiectasis.

It must be admitted that there are still certain disadvantages encountered in the application of the principles enumerated above. Chief of these is a higher incidence of bronchopleural fistula and postoperative empyema than is the case with lobectomy. In addition, some surgeons have found that a previously normal

superior segment of the lower lobes has become the site of bronchiectasis after segmental resection of diseased basal units of the lobe. This has been called traction bronchiectasis by some workers. Kergin (12) has revealed that this complication was of some moment in his patients and he has adopted a method of suturing the superior segment of the lower lobe to the adjoining segment of the upper lobe to prevent distortion and excessive traction upon this preserved segment during the process of re-expansion of the lung after surgery.

Additional instances in which segmental resection has met with wide application include certain types of solitary pulmonary cysts (figure 5), solitary metastases (figure 6), solitary tuberculomata (figure 7), quiescent, solitary pulmonary abscesses and in certain benign pulmonary neoplasms such as hamartomata and fibromata.

#### SUMMARY

1 Anatomical knowledge of the typical distribution of the pulmonary segments has been stabilized.

2 Atypical or anomalous patterns for the bronchopulmonary segments are continually under investigation and the findings are being placed in the literature and will continue to be so explored and reported.

3 A universally accepted and adopted system of nomenclature of the segments of the lungs is imperative. A plea has been made in behalf of the Jackson-Huber classification.

4 The surgical application of segmental pulmonary resection has been discussed briefly and its advantages and disadvantages have been enumerated.

#### SUMARIO

##### *Importancia Quirúrgica de la Distribución Anatómica de los Segmentos Pulmonares*

1 Nuestros conocimientos anatómicos de la distribución típica de los segmentos pulmonares han sido estabilizados.

2 Las formas atípicas o anómalas de los segmentos pulmonares se hallan continuamente en investigación, vertiéndose los hallazgos en la literatura, y continuarán siendo explorados y comunicados.

3 Un sistema de nomenclatura de los segmentos pulmonares, universalmente aceptado y adoptado, resulta imperativo. Abógase aquí por la adopción de la nomenclatura de Jackson-Huber.

4 Discútense sucintamente la aplicación quirúrgica de la resección segmentaria y sus indicaciones, limitaciones y complicaciones.

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#### *Discussion of Symposium on Segmental Pulmonary Anatomy*

Dr Norman J. Wilson, Brookline, Massachusetts. It is a real privilege to be permitted to discuss these papers of Doctors Jackson and Kent and their associates which have served to crystallize our concepts concerning the surgical and pathological anatomy of the lung. I am sure that every thoracic surgeon feels deeply indebted to them.

I should like to re-emphasize the plea which Doctor Kent made for accepting the nomenclature as outlined by Jackson and Huber. It would seem to be very essential that we all accept this standard nomenclature so that in the future we shall all talk the same language when speaking of the bronchopulmonary segments.

The localization of pulmonary pathology according to the bronchopulmonary segment involved is especially important in bronchiectasis which is a purely segmental disease process. It is also essential prior to instituting collapse therapy in tuberculous patients. At times it is impossible after collapse has been instituted to localize the pathology with accuracy. In the future, it would be ideal if internists, roentgenologists, and surgeons alike were to use the bronchopulmonary segments in expressing the location of the pathology and if this concept were taught to the medical students and resident staffs now in training.

The advantages of segmental resection are conservation of lung tissue, less overdistention, and less distortion of the remaining segments. The disadvantages of segmental resection are: (1) The fact that, technically, it is a more difficult operation than lobectomy and most operators find a higher percentage of complications, especially early in their experience with the procedure. (2) Most pulmonary lesions during the acute or exudative phase cross the boundaries of the bronchopulmonary segment and do not lend themselves safely to segmental resection. At the recent meeting of the Association of Thoracic Surgeons, Dr. Robert Shaw of Dallas pointed out the increased morbidity associated with operating on lung abscesses during the acute or subacute phase as compared with the segmental resection of chronic lung abscesses or bronchiectasis. It would seem that this would also be true of tuberculosis in the exudative phase.

Segmental resection finds its greatest usefulness in the treatment of patients with bilateral bronchiectasis where the conservation of lung tissue is imperative. It also finds a place in the treatment of chronic lung abscess, benign tumors, cysts, and tuberculomata. It has been used successfully in combination with lobectomy in the treatment of pulmonary tuberculosis, especially where the preservation of the basal segments of the lower lobe is desirable because of poor respiratory reserve or because of a contralateral lesion of questionable stability. It also is a useful procedure in removing tumors of unknown type for frozen section. If the tumor proves to be benign, nothing else is necessary. If the tumor proves to be malignant, more radical resection is indicated.

The most important technical problem is to carry out the dissection in the proper plane. The work of Boyden and other anatomists first pointed out the significance of intersegmental veins. We have been deeply indebted on our service to Dr. Beatty Ramsay whose work pointed the way to finding safely the intersegmental plane and developed a technique for working in this plane without injuring adjacent segments. The intersegmental vein is the guide to the intersegmental plane and the important technical steps are to carry out the dissection on the side of the vein of the segment which is to be removed, and to keep the plane flattened so that the adjacent segment will not become tented and subjected to injury. Prior to using this technique, the incidence of empyema at the Overholt Thoracic Clinic fell between 20 per cent and 30 per cent. This technique was first used in September 1948 and between that date and February 1949, 28 consecutive segmental resections were performed without an empyema or a serious complication.

The advent of segmental resection has created new problems which must be solved. We must turn to the clinical physiologist for help because we must be able in the future to determine objectively just how much function we are saving in the various types and combinations of segmental resections. The question also often arises as to whether or not segmental resection is preferable to lobectomy in patients with unilobar bronchiectasis. Further clinical experience and physiological studies will be required before we can know the answers to many of these problems. It would seem that we should proceed with caution in applying segmental resection to disease processes of an inflammatory nature which cross the segmental planes, such as acute suppurative disease and tuberculosis. Because we can now remove a bronchopulmonary segment with technical finesse does not necessarily mean that this is the operation or procedure of choice. It must be kept in mind that, although segmental resection is effective in the treatment of certain pathological processes, it has the potentialities of a boomerang in treating others.



# THE PHYSIOLOGICAL EFFECTS OF PNEUMOPERITONEUM UPON THE RESPIRATORY APPARATUS'<sup>2,3</sup>

GEORGE W. WRIGHT, RONALD PLACE, AND FRANK PRINCI

(Received for publication May 4, 1949)

## INTRODUCTION

The beneficial effects of pulmonary collapse have been variously explained by such factors as a diminution in pulmonary blood or lymph flow, a limitation of motion in the affected parts, stasis or hyperemia developing in the diseased tissues, and currently by a relaxation of the elastic forces present in the distended lung. Although certain of the above changes do develop in the collapsed lung, their true role has not been critically demonstrated and, in our opinion, the fundamental mechanism of the beneficial effects of collapse therapy remains an enigma. Even though acceptable proof of the *modus operandi* of collapse therapy is lacking, it is difficult to ignore the probable association between a reduction in lung size, which appears to be common to all forms of collapse therapy, and the favorable influence of this type of treatment. Moreover, a correlation between the degree of lung collapse and the effectiveness of treatment seems logical, although this also lacks critical confirmation.

The following study was undertaken in an effort to ascertain the quantitative aspect of variations in lung size consequent to pneumoperitoneum. In addition, observations concerning tidal air and minute ventilation under resting conditions were made before and after pneumoperitoneum in all cases, and in one a bronchspirometric study of the effect of pneumoperitoneum plus paralysis of the hemidiaphragm was carried out. In 10 cases, the effects of pneumoperitoneum upon the maximum breathing capacity were measured. The limited number of cases studied is regrettable, especially as to the effect of adding a paralysis of the hemidiaphragm to an established pneumoperitoneum and also as to the use of binders. Nevertheless, as the observations appear to be unique in the extant literature, and because it is not planned to pursue these investigations further in the immediate future, the limited data are published at this time.

## METHODS

The degree to which the lung is distended at any moment is closely related to the volume of gas contained therein. Variations of distention can therefore be determined by measuring the volume of air present within the lungs at a given phase of respiration. Some

<sup>1</sup> From the Department of Physiology, Edward L. Trudeau Foundation, Saranac Lake, New York.

<sup>2</sup> Presented before the Medical Section, as part of the symposium on *Laboratory and Research*, at the 45th annual meeting of the National Tuberculosis Association, Detroit, Michigan, May 4, 1949.

<sup>3</sup> This study was made possible through a grant from the Committee on Medical Research and Therapy of the American Trudeau Society, Medical Section of the National Tuberculosis Association.

consideration must be given to the fact that the volume of blood contained in the thorax will influence the gas content of the lung and is variable. If thoracic blood volume variations occur outside the pulmonary parenchyma proper, e g in the great vessels or heart, the consequent change of lung gas volume accurately represents a modification of the degree of lung distention. If, however, a variation of blood volume occurs within the parenchyma of the lung, the lung gas volume will show a concomitant change even though a modification of the degree of lung distention need not have occurred. Although a shift of blood from the abdomen and limbs into the thorax is believed to occur when the recumbent posture is assumed, there are no available data indicating the proportion which pools in the lung as opposed to the great vessels. The marked diminution in the size of the lung (during quiet breathing) that can be observed fluoroscopically to occur when the subject is changed from an erect to a recumbent position assures one that the difference in gas content of the lung measured in these two positions represents, in a large measure, a change in the degree to which the lung is distended. The elevation of intrapleural pressure known to occur when the body is shifted from the standing to the recumbent position is further evidence that this postural change reduces the degree to which the lung is distended. For present purposes and until knowledge to the contrary is presented, it appears reasonable to assume that a variation of the gas content of the lungs is indicative, though perhaps not a precise measurement, of a proportionate change in the degree of pulmonary distention.

In this communication, the volume of gas contained in the lungs at the end of a quiet expiration is termed the Functional Residual Air (FRA), at the end of a maximal expiratory effort, the Residual Air (RA), and at the end of a maximal inspiratory effort, the Total Volume (TV). The volume of gas expelled by a maximal forced expiration beginning at the mid position (end of quiet expiration) is termed Reserve Air (ReA) and is the same as the difference between the FRA and RA. The volume of gas inhaled by a maximal forced inspiration beginning at the mid position is termed Complementary Air (CA) and is the same as the difference between the TV and FRA. The complementary air added to the reserve air constitutes the Vital Capacity (VC).

The CA and ReA were determined by direct spirometry. The FRA was determined by the method of Cournand, Baldwin, Darling, and Richards (1), using pure oxygen to rinse the nitrogen from the lungs. This method was modified (and will be described in detail in a subsequent publication) to permit the subject to record his CA and ReA with a spirometer and then receive oxygen through the open circuit, thus providing a correction for the FRA and allowing true duplicates of the entire pulmonary volumina. In the experience of the present investigators, the method of Cournand *et al* has been entirely satisfactory, as it customarily provides duplicate determinations that are within a 3 per cent deviation from the mean.

The tidal air and minute ventilation were calculated from the spirometer tracings.

The Maximum Breathing Capacity (MBC) was determined by the method described by Hermanssen (5) using a specially constructed low-resistance valve and tubing (lumen 1.5 inches in diameter throughout) and expiring into a Douglas Bag. Collections of thirty seconds each were made, the volume being expressed in liters per minute (wet) at 37°C. Duplicates within 5 per cent of the mean were required.

Bronchspirometry in the single case was done as described previously (2).

#### MATERIAL AND MANNER OF STUDY

The pulmonary volumina were measured by suitable duplicates, with the subject in the standing position after being erect for twenty or more minutes, and with the subject in the recumbent position (head only elevated by a thin pillow) after lying quietly for a minimum of twenty minutes. Pre-pneumoperitoneum studies were made within a week prior to the induction of the pneumoperito-

neum Measurements during pneumoperitoneum were made in all cases forty-eight hours after the last refill and the data published herein are of the determinations made when pneumoperitoneum was considered to be fully established The intraperitoneal pressure was generally +6 to +8 cm of  $H_2O$  in those cases evidencing a "good" elevation of the diaphragm and +12 to +18 cm of  $H_2O$  in those evidencing a "limited rise" of the diaphragm Refills were usually 600 to 900 cc in volume every ten days to two weeks

The MBC was measured on the same day as the lung volume studies Bronchspirometry was carried out in the single case forty-eight hours after a refill both before and ten days after the hemidiaphragm was paralyzed

Satisfactory studies were made in the erect and recumbent positions on 17 cases and in the recumbent position only on 2 additional cases In some there was a pre-existing paralysis of the hemidiaphragm as indicated by an asterisk adjacent to the case number in table 2 In none was there evidence suggesting that there would be an impediment to the anticipated elevation of the diaphragm, except Case 19, in which severe pulmonary emphysema (RA = 57 per cent of TV) was known to be present, and Case 18, in which severe generalized pulmonary fibrosis with a small lung was associated with a diaphragm already somewhat elevated prior to the induction of pneumoperitoneum

#### OBSERVATIONS

The lung volume, MBC, and bronchspirometry data of Case 17 are presented in figure 1 and table 1 This case portrays the effects of change of body posture and of pneumoperitoneum that were observed to be common for the series of cases Of greatest interest is the effect of posture and pneumoperitoneum upon the FRA The size or state of distention of the lung for virtually the entire twenty-four hours of each day is represented by the FRA with a cyclic increase superimposed by the tidal air There are also intermittent variations of volume of a magnitude greater than the tidal air which occur during sighing, coughing, laughter, or severe physical exertion It is unfortunate that for technical reasons the lungs are customarily roentgenographed in the position of full distention, because this rarely assumed position of the lung has thus become firmly fixed in the minds of physicians as portraying *the* physiological state of the lung There would be greater clarity of thinking about the volumetric effects of collapse therapy if the fluoroscope rather than the conventional roentgenogram were more commonly used

It has been shown previously that the gas content of the lungs is diminished by changing from the erect to the recumbent posture The magnitude of this change as measured in Case 17 is indicated by comparing block  $A_1$  with  $B_1$  in figure 1, and for the series is shown in table 2, column A The mean and extremes of the change in this series are virtually identical with those of a group of 20 normal males slightly older than were previously studied in this laboratory (3) It is apparent, therefore, that recumbency is of itself actually a true form of "collapse therapy"

The establishment of pneumoperitoneum markedly diminishes the FRA in the standing position In some instances, it is as effective in this respect as is

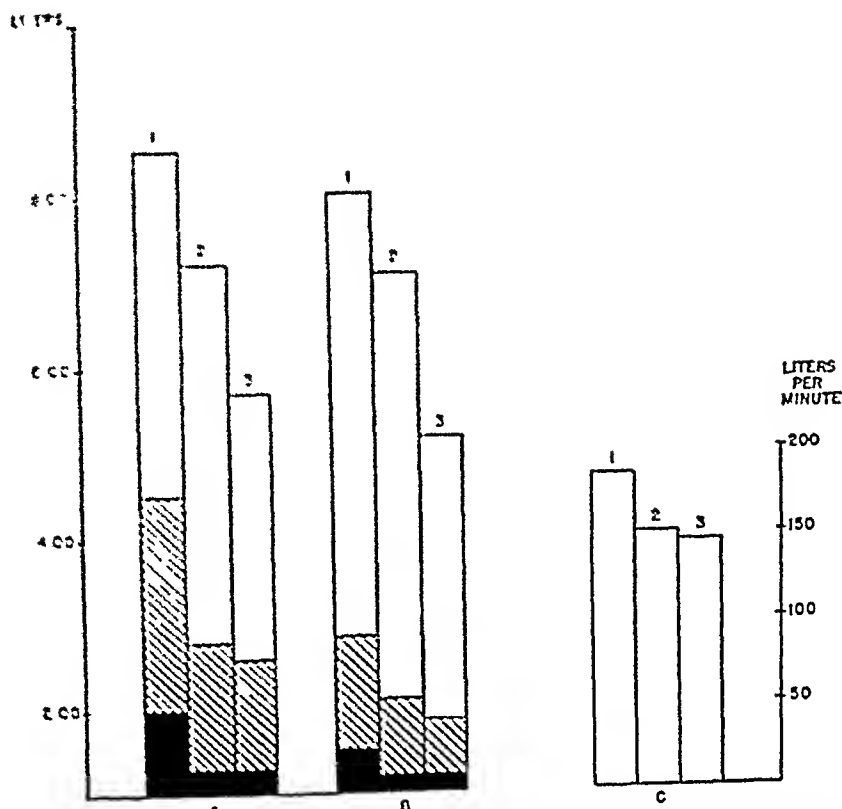


FIG 1 The effect of pneumoperitoneum and of a combination of pneumoperitoneum plus paralysis of the hemidiaphragm upon the pulmonary volumes and Maximum Breathing Capacity of Case 17

A—In the erect position

B—In the recumbent position

C—Maximum Breathing Capacity

1—Before pneumoperitoneum

2—During pneumoperitoneum

3—During pneumoperitoneum plus paralysis of the left hemidiaphragm

In A and B, the solid block is the Residual Air, the cross hatched block is the Reserve Air, and the clear block is the Complementary Air. The Functional Residual Air is made up of cross hatched plus solid blocks, and the Total Volume by all three blocks.

TABLE 1

*The Effect of Adding Paralysis of the Left Hemidiaphragm to a Pre-existing Pneumoperitoneum as Measured by Bronchspirometry*

	PNEUMOPERITONEUM ALONE		PNEUMOPERITONEUM PLUS PARALYSIS OF THE LEFT HEMIAPHRAGM	
	Right	Left	Right	Left
	<i>per cent</i>		<i>per cent</i>	
M V	64	36	74	26
O. Cons	72	28	80	20
CO. Output	67	33	78	22
V C	69	31	79	21

recumbency, a fact demonstrated by comparing  $A_2$  with  $B_1$  in figure 1. In others, it may be less effective or even more effective than recumbency alone, as shown by a comparison of columns B and A in table 2. For purposes of brevity, the complete data of the pulmonary volumes are not presented at this time. It can be

TABLE 2

*The Effect of Pneumoperitoneum and Body Posture upon the Functional Residual Air and Maximum Breathing Capacity*

CASE NUMBER	A	B	C	D	E
1	30	16	-24	42	-7
2	43	30	+10	37	
3	12	26	-30	39	-15
4*	34	43	-30	54	+4
5	44	29	-23	57	-10
6	38	49	-30	57	-13
7*	21	21	-12	30	
8	30	15	-9	36	-16
9	27	23	-27	46	-5
10	38	25	-16	48	
11	29	33	-30	51	
12	39	44	-33	59	-10
13	34	16	-13	43	
14	20	32	-26	41	
15*	28	39	-17	41	
16	40	33	0	40	+16
17	37	37	-24	52	-12
18			+6		
19			+13		-10
Mean	32	30		46	

*A* Per cent by which the Functional Residual Air was diminished when the body was shifted from the standing to the recumbent position

*B* Per cent by which the Functional Residual Air, measured with the body in the standing position, was diminished by fully established pneumoperitoneum

*C* Per cent by which the Functional Residual Air, measured with the body in the recumbent position, was altered by a fully established pneumoperitoneum. The sign indicates the direction of the change

*D* Per cent by which the Functional Residual Air, measured with the body in the standing position and without pneumoperitoneum, was diminished by a well-established pneumoperitoneum and recumbent body posture combined

*E* Per cent by which the Maximum Breathing Capacity was altered by a fully established pneumoperitoneum

\* Pre-existing paralysis of the hemidiaphragm

stated, however, that, in addition to its effect on the FRA, pneumoperitoneum also reduces the TV and RA in the erect position, although it has relatively little effect on the CA.

The FRA measured in the recumbent posture is still further diminished by the establishment of pneumoperitoneum, as demonstrated by comparing  $B_2$  with  $B_1$  in figure 1. This change occurred in 15 of the 19 cases studied, but in the other

4 there was either no further change or even a slight increase, as shown in column C, table 2. There was no apparent reason for the failure of pneumoperitoneum to cause a further diminution of the recumbent FRA in Case 16. Relatively little effect was anticipated in Case 19 because this subject has severe, diffuse, obstructive emphysema with a relaxed abdominal wall. Studies in this laboratory (3) have shown that persons with severe obstructive emphysema fail to show an appreciable reduction of the FRA upon changing from the erect to the recumbent position. The lungs simply fail to collapse, behaving under these circumstances in a manner similar to that which can be observed when the thoracic cage is opened at autopsy. As indicated in table 3, the use of a binder

TABLE 3

*The Effect upon the Pulmonary Volumina of Applying an Abdominal Binder in the Presence of Pneumoperitoneum*

	TOTAL VOLUME	VITAL CAPACITY	COMPLE- MENTARY AIR	FUNC- TIONAL RESIDUAL AIR	RESERVE AIR	RESIDUAL AIR
<i>Case 2</i>	<i>Liters</i>	<i>Liters</i>	<i>Liters</i>	<i>Liters</i>	<i>Liters</i>	<i>Liters</i>
Erect, without binder	2 95	2 08	1 61	1 34	0 47	0 87
Erect, with binder	2 69	1 76	1 57	1 12	0 19	0 93
Recumbent, without binder	2 87	1 91	1 67	1 20	0 24	0 96
Recumbent, with binder	2 50	1 57	1 38	1 12	0 19	0 93
<i>Case 14</i>						
Erect, without binder	2 45	1 72	1 37	1 08	0 35	0 73
Erect, with binder	2 30	1 46	1 22	1 08	0 24	0 84
Recumbent, without binder	2 20	1 35	1 25	0 95	0 10	0 85
Recumbent, with binder	1 99	1 05	1 02	0 97	0 02	0 95
<i>Case 19</i>						
Erect, without binder	—	—	—	—	—	—
Erect, with binder	—	—	—	—	—	—
Recumbent, without binder	6 85	3 12	2 15	4 70	0 97	3 73
Recumbent, with binder	5 04	2 50	1 82	3 22	0 68	2 54

partially remedied this lack of pneumoperitoneum effect upon the FRA in Case 19. The failure to diminish the recumbent FRA in Case 18, in spite of an intra-abdominal pressure of 20 cm. of  $H_2O$ , is not clear. This patient had a very extensive fibrosis diffusely distributed throughout both lungs which was apparently the residuum of extensive tuberculosis. There was no clear evidence of severe obstructive emphysema and the MBC and the RA expressed as a per cent of TV were only slightly abnormal. The diaphragm was elevated and moderately limited in mobility. Some obscure factor prevented the anticipated further elevation of the diaphragm. The failure to establish a further diminution of the recumbent FRA in Case 2 appeared related to the fact that the anterior abdominal wall was very flabby and lacking in tone as a result of multiple pregnancies. The patient would not wear a binder or tolerate high pressures.

In the recumbent position, pneumoperitoneum reduced the TV and also the RA but had only a slight effect upon the CA. The marked change in lung size that resulted from a combination of recumbency and pneumoperitoneum is ap-

parent in the contrast of  $B_2$  and  $A_1$  in figure 1 and by inspection of column D in table 2. This comparison reveals the most impressive effect of pneumoperitoneum upon the pulmonary volumina.

The effects of paralysis of the hemidiaphragm added to an established pneumoperitoneum were observed in Case 17 and are shown in figure 1,  $A_3$  and  $B_3$ , and in table 1. The RA was not appreciably altered in either the erect or recumbent posture. The FRA was measurably, though not strikingly, diminished in both positions. The most marked change occurred in the CA which was reduced by 1.49 liters in the standing position and 1.76 liters in the recumbent position. Bronchspirometric studies made before and after the addition of a left hemidiaphragm paralysis in Case 17 are shown in table 1. Although the extent to which the left lung participates in each breath is measurably reduced by the paralysis, the ribs are apparently still an effective means of bringing about a cyclic distention of the left lung. The effects of paralysis of the hemidiaphragm upon the pulmonary volumina and the dynamics of respiration appear to be the same in this case with a pneumoperitoneum as when the paralysis is induced in the absence of pneumoperitoneum. The size of the lungs *at the end of quiet expiration* is little if at all affected by the paralysis, but the lung on the paralyzed side is distended to a lesser extent with each ordinary breath and is further protected, although not entirely so, from periodic distention by deep breaths. The effects of pneumoperitoneum and paralysis of the hemidiaphragm in this single case (supported by fluoroscopic and roentgenographic confirmation in this and other cases) were additive.

The effect of applying a tight abdominal binder to an established pneumoperitoneum was studied in Cases 2, 14, and 19. The data are shown in table 3. There was relatively little further change in the pulmonary volumina of Cases 2 and 14, but quite a large change in all divisions of the volumina was observed in Case 19. As noted earlier, pneumoperitoneum alone produced virtually no change in the lung size of Case 19. Since the diaphragm was low even in the presence of the pneumoperitoneum, the tightly applied binder had an opportunity to bring about an elevation of the diaphragm and thus effect a diminution of the pulmonary volumina. In Case 14, and to a lesser extent in Case 2, the diaphragm was already elevated as a result of the pneumoperitoneum plus the recumbent position, and a binder had little chance to force the diaphragm to a further elevation.

The effect of pneumoperitoneum on the MBC is shown in table 2. In general, the reduction is relatively slight. This finding is readily explainable in view of the fact that a loss of stroke volume can be compensated for over a quite wide range by an increase of the number of breaths made in the 30 seconds allotted for the test (made possible because each stroke is smaller). These results confirm the data of Steinlin (4) who also observed only a slight reduction of the MBC in pneumoperitoneum.

The tidal air and minute ventilation measured at rest were not appreciably changed by the establishment of pneumoperitoneum. Minor variations were noted but were inconstant and thought to be within the range of variations for untrained subjects.

## COMMENT

Pneumoperitoneum, if fully established, is an effective method of reducing the size or state of distention of the lung. In this respect, it is more adequate than paralysis of the hemidiaphragm. Since the modern concept of the degree of collapse desired in intrapleural pneumothorax commonly makes use of less than a 50 per cent collapse of the lung, pneumoperitoneum plus recumbency is just as effective in collapsing the lung as is pneumothorax, unless virtually complete collapse of the lung is desired.

The addition of a paralysis of the hemidiaphragm to an established pneumoperitoneum in the single case studied affected the FRA only slightly, but did reduce the cyclic distention of the homolateral lung caused by quiet respiration and partially protected it against periodic deep breaths. This finding should in no way be construed to invalidate the use of hemidiaphragm paralysis in combination with pneumoperitoneum. It should indicate clearly, however, the need for more study of this combination of therapeutic methods, and seriously raises a question about their routine simultaneous use.

The application of an abdominal binder as an adjunct to pneumoperitoneum deserves further study. If the lungs are already reduced in volume and the diaphragm has ascended in the thorax to the limit imposed by factors intrinsic in the muscle itself, little seems likely to be further accomplished by a binder. If, however, the lung has not been appreciably reduced in volume because of intrinsic pulmonary factors or a lax abdominal wall, a binder might be of considerable aid in further collapsing the lung.

That pneumoperitoneum affects both lungs equally seems apparent from inspection of the roentgenograms taken at various phases of breathing. Actual measurements of the roentgenographic changes in this series of patients may be published at a later date. It is possible, but as yet unproved, that the addition of a paralysis of the hemidiaphragm may selectively reduce the size of the homolateral lung in comparison to its contralateral mate. Inspection of the roentgenograms taken at the end of quiet expiration in the recumbent position shows little evidence of such a selective change.

Since the pulmonary volumina of the erect person with a pneumoperitoneum closely simulate those of a recumbent person without pneumoperitoneum, it is tempting to think that pneumoperitoneum might be used as a substitute for recumbency when the latter is not feasible. The enhanced effect of the reduction of lung size when recumbency is added to pneumoperitoneum indicates the advantages of recumbency when feasible.

The relatively slight reduction of MBC that results from pneumoperitoneum, together with the fact that it is a reversible form of treatment, makes it possible to use this form of collapse therapy in cases of severe respiratory crippling.

## SUMMARY

Pneumoperitoneum causes a marked reduction in the functional residual air, residual air, and total volume of a subject in the erect position. A similar though quantitatively less marked effect is observed when the subject is studied in the recumbent position.



The effects upon the pulmonary volumina and proportion of respiration performed by each lung (bronchspirometry), produced by adding a paralysis of the hemidiaphragm to a pre-existing pneumoperitoneum, were observed. A small further reduction of functional residual air and a large reduction of complementary air, together with a reduction in function by the homolateral lung, resulted from the added paralysis.

An abdominal binder caused a slight diminution of pulmonary volumina in two cases and a marked diminution in a third case when applied in the presence of pneumoperitoneum.

The maximum breathing capacity was only slightly reduced by the induction of pneumoperitoneum.

#### SUMARIO

##### *Efectos Fisiológicos del Neumoperitoneo sobre el Aparato Respiratorio*

El neumoperitoneo provoca marcada disminución del aire residual funcional, el aire residual y el volumen total en un sujeto en posición erecta. Obsérvase un efecto semejante, pero cuantitativamente menos pronunciado, cuando se estudia al sujeto, recostado.

Estudióse también el efecto sobre los volúmenes pulmonares y la proporción de respiración ejecutada por cada pulmón (broncoespirometría), producido al sobreponer una parálisis del hemidiafragma a un neumoperitoneo preexistente. La parálisis sobrepuesta agregó una pequeña reducción del aire residual funcional y una gran reducción del aire complementario, junto con una disminución de la función del pulmón homolateral.

Una faja abdominal ocasionó una leve disminución de los volúmenes pulmonares en dos casos y una pronunciada disminución en otro caso, cuando se aplicó en presencia de un neumoperitoneo.

La capacidad respiratoria máxima apenas descendió por virtud de la inducción del neumoperitoneo.

#### *Acknowledgment*

The excellent cooperation of the patients who volunteered for this study is deeply appreciated. We are grateful also to the physicians of the Trudeau Sanatorium staff, especially Dr. Roger S. Mitchell, for their invaluable aid in making these observations.

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# EVALUATION OF STREPTOMYCIN REGIMENS IN THE TREATMENT OF TUBERCULOSIS<sup>1,2</sup>

An Account of the Study of the Veterans Administration, Army and Navy July 1946 to April 1949

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## INTRODUCTION

The cooperative investigation of the effect of streptomycin in the treatment of tuberculosis by the Veterans Administration, Army, and Navy began in July 1946. The cooperating investigators have abided by common protocols mutually agreed upon governing indications for treatment, observations of results, and methods of reporting results (1). Beginning with the study of pulmonary tuberculosis, the investigation was gradually extended until, at the end of its first year, all types of tuberculosis were included in its range. Comprehensive progress reports of the study have appeared on two occasions (2, 3).

The general objective of the study has been to determine the efficacy and the indications of streptomycin in the treatment of tuberculosis. Originally, relatively high daily doses, 15 or 20 Gm., were employed for 120 days. This stage of the investigation confirmed the observation that streptomycin exerts a favorable effect on the course of tuberculosis in man (1). In subsequent stages of the investigation variations of the original regimen have been explored, such as lower daily dosages, shorter periods of administration, and reduction in the number of daily injections into which the total daily dose is divided. To date, streptomycin therapy has been completed in approximately 4,500 cases, exclusive of courses of treatment given for relatively short periods of time before and after certain surgical procedures. Approximately 2,000 cases of pulmonary tuberculosis have been treated.

The purpose of this paper is to summarize certain aspects of this cooperative investigation since its inception, particularly with reference to the effect that variations in streptomycin regimen have had upon toxicity, the emergence of streptomycin-resistant strains of *M. tuberculosis*, and suitable clinical observations. Primary emphasis will be placed upon the results of streptomycin treatment of pulmonary tuberculosis.

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<sup>2</sup> Presented before the Medical Section, as part of the symposium on *Streptomycin and Tuberculosis*, at the 45th annual meeting of the National Tuberculosis Association, Detroit, Michigan, May 3, 1949.

<sup>3</sup> Presented in part before the Seventh Streptomycin Conference, Veterans Administration, Denver, Colorado, April 22, 1949.

<sup>4</sup> Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

## METHODS

*Administrative control* Original plans for the investigation were formulated by representatives of the Veterans Administration, Army, and Navy in May 1946, with the advice of representatives of the Public Health Service, the National Research Council, and the National Tuberculosis Association (1). Continuity has been provided through a Streptomycin Committee of the Central Office, Veterans Administration. As the study has progressed, committees from among the investigators and the consultants to the study have been appointed by the Streptomycin Committee, and since 1947 all decisions as to the course of the investigation have been the result of committee recommendations which were approved by the cooperating investigators. The Streptomycin Committee has continued to be responsible for administration of the program in the intervals between semiannual Conferences which were held for the evaluation of results and for planning the future course of the study.

*Liaison between study units* Representatives of the Streptomycin Committee have visited all or most of the cooperating Study Units. Study Units have submitted monthly progress reports of their experience (bi monthly since April 1948) which have been mimeographed and distributed to cooperating investigators. Streptomycin Conferences, of which there have been seven, have been held at intervals of approximately six months, to which all participating investigators, as well as consultants and other individuals interested, have been invited. In this manner there has been assured a considerable uniformity in the type of case treated, in the conditions of treatment, and in the observation and recording of results.

*Introduction of variations of streptomycin regimen*

- 1 July 1946 1.8 Gm a day (0.3 Gm every 4 hours), later 2.0 Gm (0.4 Gm every 4 hours 8 a.m. to midnight), for 120 days, employed in seven Study Units, increased to twenty-one Study Units in December 1946, all forms of tuberculosis
- 2 May 1947 2.0 Gm a day (0.4 Gm every 4 hours 8 a.m. to midnight), for 60 days, in seven Study Units, pulmonary tuberculosis only
- 3 May 1947 1.0 Gm a day (0.2 Gm every 4 hours 8 a.m. to midnight), for 120 days, in seven Study Units, all forms of tuberculosis
- 4 May 1947 1.0 Gm a day (0.5 Gm every 12 hours) for 120 days, in seven Study Units, all forms of tuberculosis
- 5 October 1947 0.5 Gm a day (0.25 Gm every 12 hours) for 120 days, in seven Study Units, pulmonary and laryngeal tuberculosis, and draining tuberculous sinuses only
- 6 April 1948 1.0 Gm a day (0.5 Gm every 12 hours, changed to 1.0 Gm in a single dose daily in October 1948) for 42 days, all Study Units, all forms of tuberculosis
- 7 April 1948 0.5 Gm a day (0.25 Gm every 12 hours, changed to 0.5 Gm in a single dose daily in October 1948) for 42 days, in the majority of forty-eight Study Units, nearly all forms of tuberculosis
- 8 April 1948 0.2 Gm a day (in a single injection) for 120 days, and for 42 days, in six Study Units, tuberculous draining sinuses only
- 9 October 1948 1.0 Gm a day (in a single injection) (2.0 Gm a day in a single Study Unit) every third day for 120 days, eight Study Units, pulmonary tuberculosis only
- 10 December 1948 2.0 Gm a day of *dihydrostreptomycin* (1.0 Gm every 12 hours) for 42 days, all Study Units, all forms of tuberculosis
- 11 Variations have been permitted in the treatment of military and meningeal tuberculosis, but the majority of these cases have been treated with 2.0 Gm a day for 120 days or longer

*Random selection of cases on different streptomycin regimens* It was the original decision of the Streptomycin Committee to have the Study Units select suitable cases and then divide them at random into two groups, the one to be treated with streptomycin, the other to serve as controls. Adequate clinical material was not found to be available, and this plan was abandoned (1). The investigation of the original streptomycin regimen, 1.8 Gm a day (later 2.0 Gm a day) for 120 days provided no "controls" in the strict sense of comparing

treated cases with untreated cases. Beginning in May 1947, three regimens were investigated simultaneously, although each regimen was employed in only one Study Unit. Since April 1948, there has been alternation of cases in most Study Units according to a statistically satisfactory method of random selection.

*Methods of reporting results.* In the early stages of the study, results reported by investigators were pooled and compiled at the Streptomycin Conferences and reported in the *Minutes* of the first three Conferences. For the Fourth Conference (St. Louis, October 9-12, 1947) (1) a beginning was made in the assembling of data in tabular form. For subsequent Conferences pertinent data have been assembled from the Study Units in advance of the meetings and collected by the Streptomycin Committee for distribution to members of the Conferences (5, 6, 7). These compilations have been in summary tabular form, permitting relatively little cross tabulation of the effect of various variables, but for the Seventh Conference (Denver, April 21-24, 1949) (7) data on cases of pulmonary tuberculosis were assembled on simplified individual case report forms, permitting the reporting of a number of pertinent cross tabulations. Since February 1948, a committee appointed by the Streptomycin Committee has been in the process of developing individual case report forms for the major portion of cases treated. The first of these forms, for pulmonary tuberculosis and for military tuberculosis and tuberculous meningitis, were distributed in May 1949. Results so reported are to be analyzed and processed with the assistance of the Medical Research Statistics Division, Central Office, Veterans Administration, permitting a range of interpretation considerably wider than that which has been possible thus far. Results presented in this paper are derived almost entirely from data reported to the last three Conferences (5, 6, 7).

*Reporting of change in tuberculous condition treated.* In the absence of more objective criteria, investigators have been asked to report the results of streptomycin therapy not only in such terms as "improved" (and "healed" according to stipulated criteria), "unchanged", and "worse", but in different degrees of improvement and worsening. A "scale" which has been found to be practicable and to have a considerable degree of consistency of result has now been adopted. In employing the scale, investigators are requested to make every effort to assign uniform weighting to each point on the scale. The scale, which will also be employed in the individual case report forms, is as follows:

- 1 marked improvement
- 2 moderate improvement
- 3 slight improvement
- 4 no change
- 5 slight worsening
- 6 moderate worsening
- 7 marked worsening

For the Fifth Streptomycin Conference (5), changes were reported on a nine-point scale, which included extremes of very marked improvement and very marked worsening, but the simpler seven-point scale has now been adopted.

*"Jury" reviews.* Desiring to increase the objectivity of the observation of results, on two occasions investigators have been requested by the Streptomycin Committee to submit roentgenograms of treated cases of pulmonary tuberculosis to an impartial "jury" of experts for re-evaluation. The results of these two reviews have been reported (1, 5).

*Statistical interpretations.* The nature of the data and of the method of reporting has not permitted elaborate statistical analysis of results. It has not been possible to employ means, standard deviations, tests for the significance of the difference of means, or the analysis of variance. Reporting of results in terms of percentage of total samples has, however, permitted the use of the chi square test, and this test has been employed in this paper where the data have been regarded as suitable. Where statements are made as to the "significance" of differences noted, it is understood that the probability of the difference being due to chance, as determined by the chi square test, is less than 0.05 (less than one chance in twenty).

## OBSERVATIONS

*Toxicity*

It is now well known that the course of the Good Ship Streptomycin lies between the Scylla of toxicity and the Charybdis of bacterial resistance. Fortunately both of these navigational hazards have now been well charted.

In figures 1, 2, and 3 may be seen the incidence of the more important toxic manifestations present among patients treated on seven different streptomycin regimens. In figure 1 the differences for the incidence of vertigo are significant among the cases treated on the first five streptomycin regimens, 2.0 Gm. a day

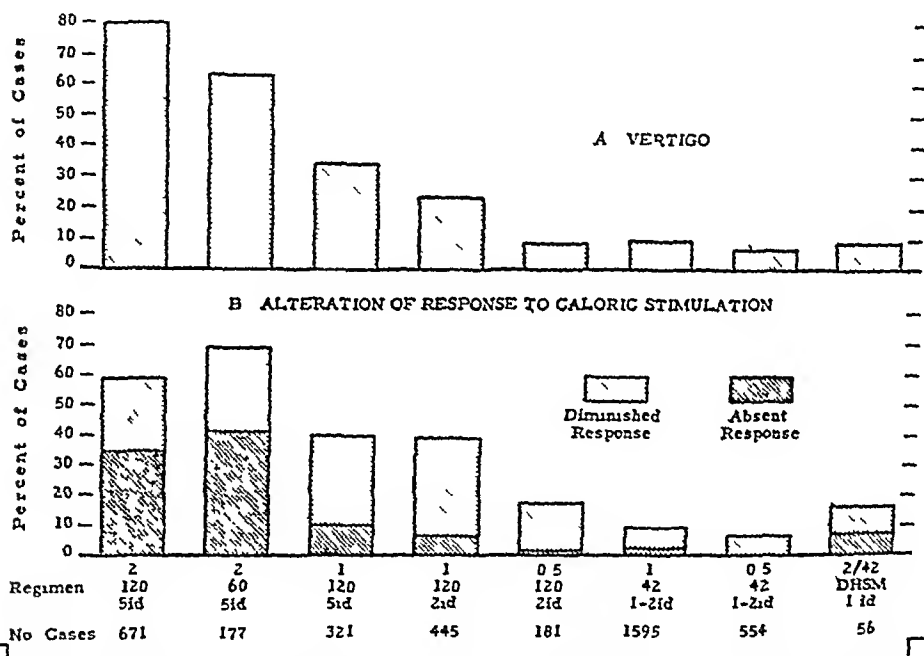


FIG. 1. Incidence of vestibular toxicity on various streptomycin regimens (during treatment period).

for 120 days<sup>5</sup>, 2.0 Gm. a day for 60 days, 1.0 Gm. a day for 120 days (with both 5 and 2 injections a day), and 0.5 Gm. a day for 120 days. The differences are not significant among the cases treated on the following regimens: 0.5 Gm. a day for 120 days, 1.0 Gm. a day for 42 days, and 0.5 Gm. a day for 42 days. Much the same differences are noted in figure 1 for altered response, both diminished and absent, to caloric stimulation (by the modified Kobrak technique), except that the differences between the two 1.0 Gm. a day for 120-day regimens are not significant. These figures clearly establish that, as the daily dose of streptomycin is reduced from 2.0 to 1.0 to 0.5 Gm. a day, with duration constant at 120 days,

<sup>5</sup> Hereafter the regimen so designated will also be understood to include cases treated with 1.8 Gm. a day for 120 days.

there is significantly less vestibular toxicity, that, as duration of streptomycin therapy is shortened from 120 to 60 or 42 days there is less vestibular toxicity, although this decrease is less than in the case of reduction in the daily dose, and that, in the case of vertigo, reducing the number of injections of streptomycin per day, without otherwise altering the 1.0 Gm a day for 120-day regimen, decreases toxicity somewhat.

In figure 2 may be seen the data for the incidence of certain manifestations of renal toxicity. Differences reported in diminished renal function are not significant among cases treated on the four regimens of higher total dosage nor among those treated on the three of smaller total dosage, but on the three latter (those

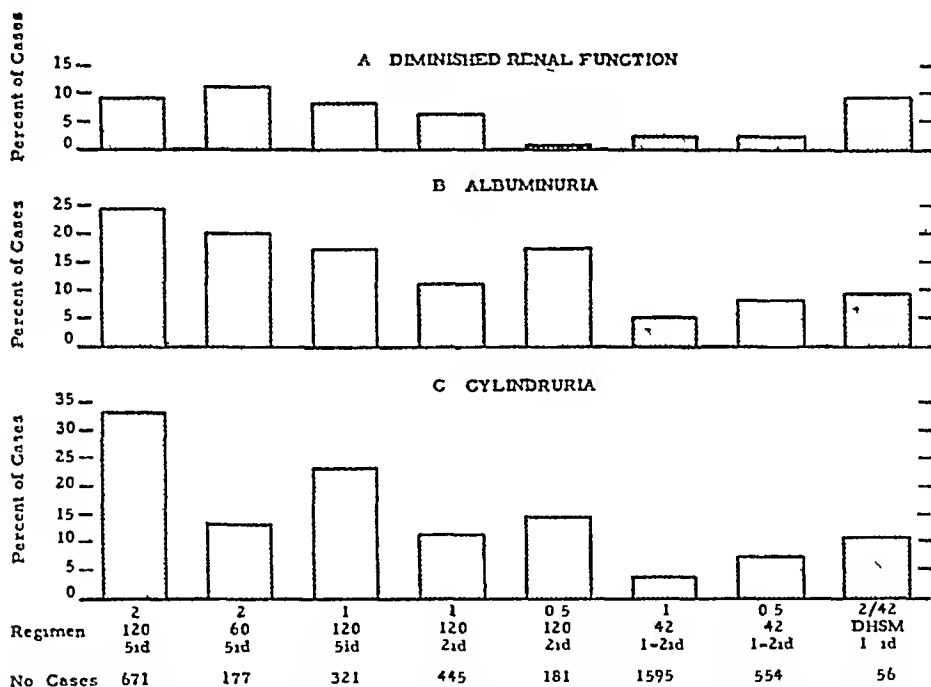


FIG. 2 Incidence of renal toxicity on various streptomycin regimens (during treatment period)

of 0.5 Gm a day for 120 days, and 1.0 Gm or 0.5 Gm a day for 42 days) there is significantly less interference with renal function than among patients treated on the first four regimens. With respect to albuminuria and cylindruria, the data in figure 2 suggest that streptomycin regimens of longer duration are more often associated with a high incidence of toxicity than are those with larger daily dosages. The effect of reducing streptomycin dosage, through reduction in daily dosage, or duration, or number of daily injections, is less in the case of renal toxicity than in the case of vestibular toxicity.

The incidence of dermatitis, both mild and severe (figure 3), associated with streptomycin therapy, appears to be more related to duration of therapy than to daily dosage. Dermatitis is found to be present with significantly greater fre-

quency among patients treated on regimens of longer duration (120 days) than in patients treated for a shorter period (60 or 12 days), whether the daily dose is 2.0 Gm., 1.0 Gm. or 0.5 Gm. With respect to drug pyrexia (figure 3), there is significantly greater toxicity only in the case of the patients treated on the first regimen, that of 2.0 Gm. a day for 120 days.

In figure 3 are also presented the data for the frequency with which serious toxicity makes it necessary to terminate streptomycin therapy. There is found to be a significantly more frequent occurrence of this development between the two 2.0 Gm. a day regimens and the other five, and between the 1.0 Gm. a day for 120-day regimen in 5 divided doses and the remaining four.

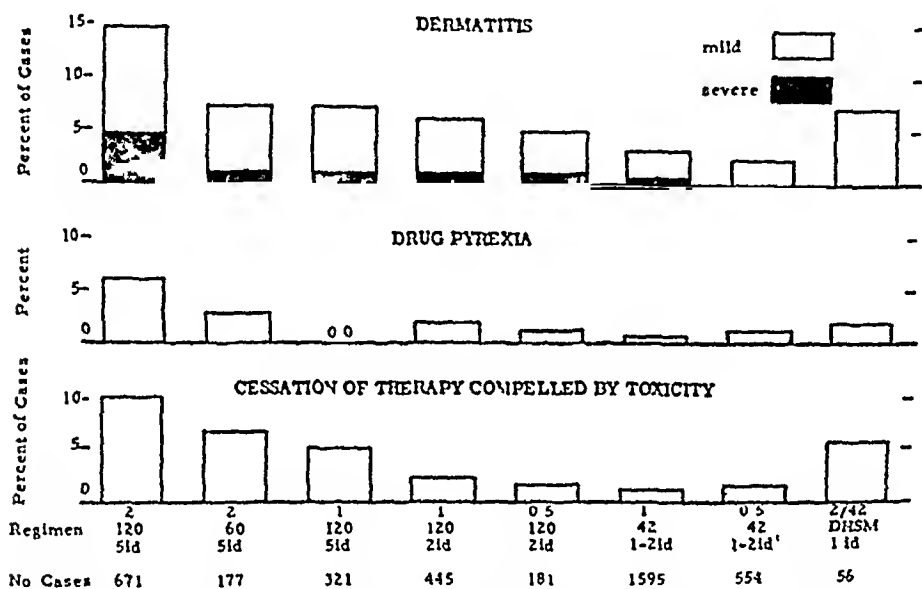


FIG 3 Incidence of other toxicity on various streptomycin regimens (during treatment period)

The data presented in figures 1, 2, and 3 are summarized in table 1 which also includes the respective incidences of other toxic manifestations which are of lesser frequency and importance. From this evaluation it may be stated that, in general, there has been a reduction of streptomycin toxicity with the following modifications of streptomycin regimens, listed in the order of their importance: (a) reduction in daily dosage, (b) reduction in duration of therapy, and (c) decrease in the number of daily injections into which the total daily dose is divided. The effect of each of these variables has differed with the particular toxic manifestation studied.

The data for these toxic manifestations are based upon observations during the treatment period. Follow-up data on some of the manifestations have been reported to the last three Streptomycin Conferences (5, 6, 7). These data indicate that, whereas there is little change six months or more after the end of treatment

TABLE 1  
Incidence of Toxicity to Streptomycin on Various Regimens

Regimen { Daily dose Duration No. Inj./d	SM 2 Gm 120 days 5 i/d		SM 2 Gm 60 days 5 i/d		SM 1 Gm 120 days 5 i/d		SM 1 Gm 120 days 2 i/d		SM 0.5 Gm 120 days 2 i/d		SM 1 Gm 42 days 1-2 i/d		SM 0.5 Gm 42 days 1-2 i/d		DHSM 2 Gm 42 days 2 i/d	
	671 (5)		167 (5*)		321 (5*)		445 (5*)		181 (6*)		1595 (7*)		554 (7*)		56 (7*)	
Toxic Manifestation	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
<b>1 Toxicity Caused</b>																
a Cessation therapy	67	9.9	11	6.4	16	5.0	9	2.0	3	1.7	19	1.2	8	1.4	3	5.4
b Interruption therapy	32	1.8	6	3.4	10	3.1	9	2.0	2	1.1	13	0.8	7	1.3	2	3.6
<b>2 Vestibular</b>																
a Vertigo	537	80.0	111	62.7	110	31.3	103	23.1	16	8.8	151	9.8	40	7.2	5	8.9
b Ataxia (ataxia tested)	302	45.0	16	26.0	66	20.6	51	11.5	7	3.9	10	5.1	13	1.0	7	17.5
	(**)		(**)		(**)		(**)		(**)		(737)		(323)		(10)	
c c s r * dimin	170	25.3	19	27.7	96	30.0	105	23.4	29	16.0	66	7.0	23	6.1	4	9.1
d c s r absent	229	31.1	73	41.2	33	10.3	24	5.4	2	1.1	15	1.6	1	0.2	3	6.8
e c s r altered (e s tested)	399	59.1	122	68.9	129	40.3	129	28.8	31	17.1	81	5.6	21	6.3	7	15.9
	(**)		(**)		(**)		(**)		(**)		(938)		(377)		(44)	
<b>3 Auditory Loss</b>																
a to spoken voice	18	2.7	1	0.6	1	0.3	1	0.2	0	0.0	7	0.4	1	0.2	2	4.5
b audiom, high range	61	9.1	26	14.7	9	2.8	31	7.0	2	1.1	57	5.4	26	6.2	2	4.5
c audiom, low range (tested by audiom)	32	4.7	8	4.5	4	1.2	11	2.5	0	0.0	11	1.0	9	2.1	2	4.5
	(**)		(**)		(**)		(**)		(**)		(1,059)		(419)		(44)	
<b>4 Renal Function</b>																
a dimin, inter- mittent	43	6.4	6	3.4	24	7.5	19	4.3	0	0.0	25	1.6	8	1.4	1	1.8
b dimin, main- tained	19	2.8	13	7.4	1	0.3	7	1.5	1	0.6	12	0.8	4	0.7	4	7.1
c dimin, int and maint	62	9.2	19	10.8	25	7.8	26	5.8	1	0.6	37	2.4	12	2.1	5	8.9
d cylindruria	223	33.2	23	13.0	74	23.1	48	10.8	26	14.4	53	3.3	38	7.0	6	10.7
e albuminuria	164	24.4	34	19.8	55	17.1	49	11.0	31	17.1	81	5.1	44	8.1	5	8.9
f hematuria	54	8.0	23	13.0	9	2.8	12	2.7	21	11.6	28	1.8	16	2.9	2	3.6
<b>5 Dermatitis</b>																
a mild	67	10.0	10	5.6	18	5.6	21	4.7	7	3.9	44	2.8	12	2.2	4	7.1
b severe	31	4.6	2	1.1	4	1.2	5	1.1	2	1.1	8	0.5	0	0.0	0	0.0
c all	98	14.6	12	6.7	22	6.8	26	5.8	9	5.0	52	3.3	12	2.2	4	7.1
<b>6 Other</b>																
a eosinophilia (>6%)	426	63.5	87	49.2	118	36.8	154	34.6	60	33.1	206	12.9	82	14.8	15	26.8
b blood dyscrasia	4	0.6	4	2.3	3	0.9	3	0.7	0	0.0	3	0.2	1	0.2	1	1.8
c paresthesia	120	17.9	4	2.3	13	4.1	16	3.6	6	3.3	25	1.6	5	0.9	7	12.5
d nausea and vomiting	111	16.5	7	7.9	9	2.8	22	4.9	3	1.7	26	1.6	12	2.2	6	10.7
e fever	38	5.7	5	2.8	0	0.0	8	1.8	2	1.1	6	0.4	6	1.1	1	1.8
f psychosis	14	2.1	1	0.6	5	1.6	1	0.2	0	0.0	3	0.2	0	0.0	0	0.0

\* Identifies number of Streptomycin Conference from Minutes of which data are obtained

\*\* Information not available

\* c s r = caloric stimulation response

SM = streptomycin

DHSM = dihydrostreptomycin



in diminution of response to caloric stimulation, or in ataxia, the incidence of subjective vertigo is generally less than half that present during treatment. Follow-up data with respect to auditory function six months or more after the end of therapy indicate that slightly less disability is present, audiometrically and to the spoken voice. Late increase in the incidence of these toxic manifestations has not been observed in this study.

**Dihydrostreptomycin** Dihydrostreptomycin, in doses of 2.0 Gm a day for 42 days, has been employed by the Study only for the past four months. At the Seventh Streptomycin Conference, toxicity data were reported for this hydrogenated product of streptomycin on the basis of 56 cases. The results are reported in figures 1, 2, and 3 and in table 1.

The more important toxic manifestations are summarized in table 2. In this table, by comparing the toxic manifestation of dihydrostreptomycin on a regimen of 2.0 Gm a day for 42 days, in the middle column, with that of streptomycin on

TABLE 2  
*Comparison of Toxicity of Streptomycin and Dihydrostreptomycin*

Drug* Regimen† Number of Cases	SM 2/60 177	DHSM 2/42 56	SM 1/42 1,595
Toxic Manifestation	(Per cent of Cases)		
Vertigo	62.7†	8.9§	9.8
Altered response to caloric stimulation	68.9†	15.9†	8.6
Dimin. renal function	10.8§	8.9†	2.4
Dermatitis	6.7§	7.1†	3.3
Cessation of therapy compelled by toxicity	6.4§	5.4†	1.2

\* SM = streptomycin, DHSM = dihydrostreptomycin.

† Numerator of fraction designates daily dose in grams, denominator duration of treatment in days.

‡ Difference between adjacent pairs statistically significant.

§ Difference between adjacent pairs not statistically significant.

a regimen of 2.0 Gm a day for 60 days, to the left, it is possible to approximate a dose-for-dose comparison of the two drugs. A similar comparison based on identical periods of therapy may also be made by comparing the incidence of toxicity on a streptomycin regimen of 1.0 Gm a day for 42 days with a 42-day dihydrostreptomycin regimen of 2.0 Gm daily.

As the symbols for the statistical significances of the differences indicate in table 2, with dihydrostreptomycin there appears to be definitely less vestibular toxicity than with streptomycin, but no less impairment of renal function, dermatitis, or frequency with which toxicity causes cessation of therapy, when the two drugs are compared dose for dose. When streptomycin and dihydrostreptomycin regimens of the same duration are compared, 2.0 Gm a day of dihydrostreptomycin is found to be associated with significantly more toxicity than 1.0 Gm a day of streptomycin, except that the reported incidence of vertigo is not significantly different. These preliminary data therefore suggest that dihydrostrepto-

mycin is less toxic with respect to vestibular function, but not less toxic than streptomycin with respect to the other toxic manifestations mentioned. The number of cases treated with dihydrostreptomycin is small and it is anticipated that data reported to the next Streptomycin Conference will clarify the picture of the relative toxicities of the two related antibiotics.

### *Sensitivity of Tubercle Bacilli to Streptomycin*

Throughout the streptomycin investigation, emphasis has been placed on determinations of sensitivity of tubercle bacilli recovered from patients before, during, and after completion of streptomycin therapy. Determinations were made at first in liquid media, more recently on solid media. Good comparability

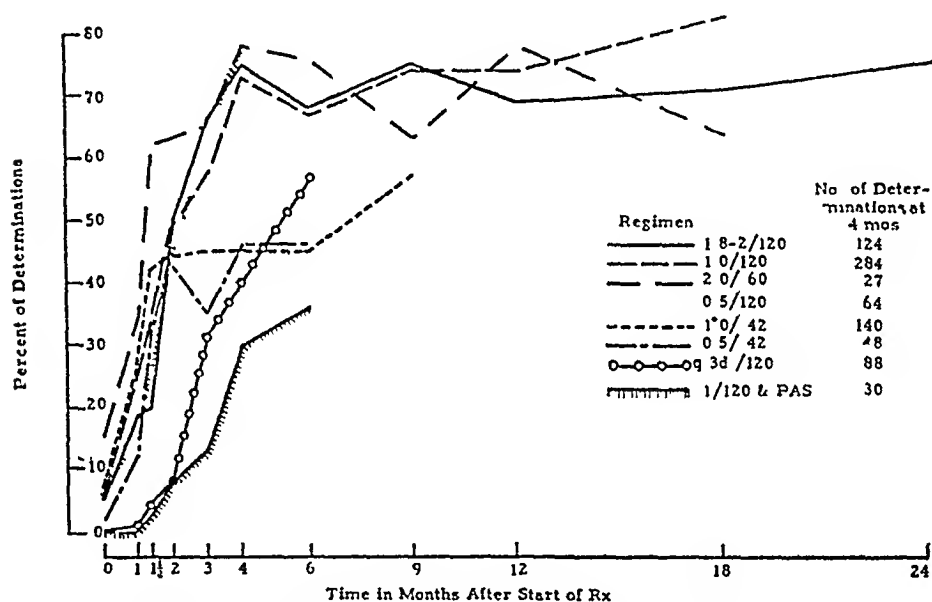


FIG 4 Percentage of organisms resistant to 10  $\gamma$  of streptomycin per ml or more on various streptomycin regimens, at different times after start of therapy

of results was found, and the results for the two methods combined are presented in figure 4, in the case of tubercle bacilli which proved to be resistant to 10  $\gamma$  or more of streptomycin per ml.

Differences for the three 120-day regimens (2.0 Gm, 1.0 Gm, and 0.5 Gm of streptomycin daily) of daily administration are not statistically significant, nor do significant differences exist between these data and those obtained from the 2.0 Gm a day for 60-day regimen. Differences likewise are not significant between the two 42-day regimens. As a consequence, the percentages of resistant organisms for regimens of identical duration have been combined and are presented in figure 5.

Disregarding the daily dosage of streptomycin, it appears that there is definitely less emergence of resistant tubercle bacilli on a regimen of 42 days than on

regimens of either 60 or 120 days. The cumulative rates for the emergence of tubercle bacilli resistant to 10  $\gamma$  per ml or more when streptomycin was administered daily appear to be first month, 20 per cent, second month, 50 per cent, third and fourth months, 62.5 and 75 per cent, respectively. Interpolations for regimens of other duration may be made between these points with a fair degree of accuracy.

Data have also been gathered for the percentage of organisms resistant to 100  $\gamma$  of streptomycin per ml or more. Figure 6 presents these data for approximately 500 cases treated on the 120-day regimens, in comparison with the resistance data for the 10  $\gamma$  per ml level. As may be seen, there is a fairly close parallel between the two rates, although they are at two levels, significantly different from each other.

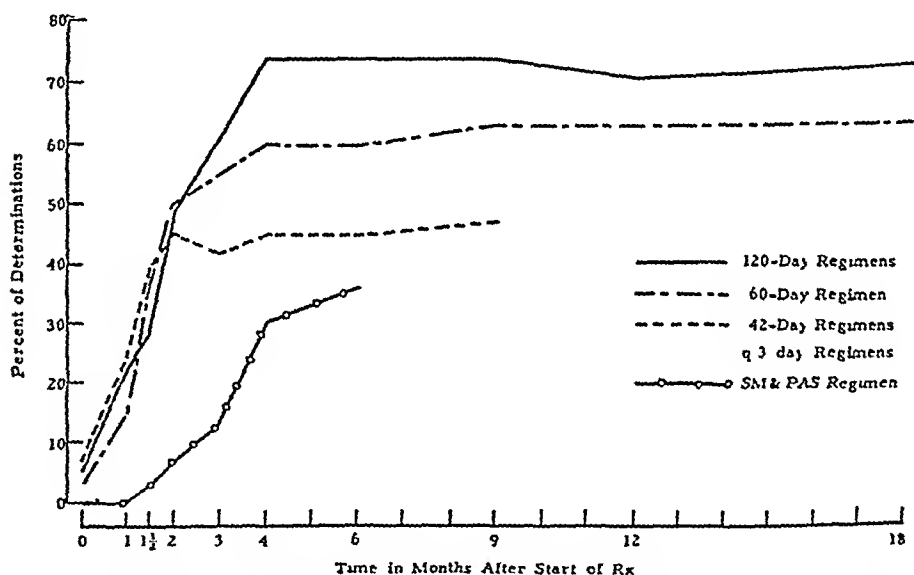


FIG. 5. Percentage of organisms resistant to 10  $\gamma$  of streptomycin per ml or more on various regimens, at different times after start of therapy.

In figure 5, data are also presented for the rate of emergence of tubercle bacilli resistant to 10  $\gamma$  or more of streptomycin per ml on a regimen of 1.0 Gm administered every third day for 120 days. On this regimen, the rate of emergence of resistance *per day of treatment* appears to approximate closely that of daily injection, being, on the every-three-day regimen, one-third the rate of that with daily administration. Differences for this regimen from the data for the first three regimens (120, 60, and 42 days) are significant at all points in time up to 4 months after the start of therapy. Moreover, significant differences also exist at four months between these data (every-three-day regimen) and the values obtained from the 120-day and 60-day regimens.

Also shown in figure 5 are data for the rate of emergence of tubercle bacilli resistant to 10  $\gamma$  of streptomycin per ml on a combined regimen of 1.0 Gm of

streptomycin daily and 9 to 15 Gm daily of para-aminosalicylic acid (PAS) The percentages of organisms resistant on this regimen are significantly lower than in the case of regimens of daily streptomycin administration without PAS for all points in time except six months after the start of treatment, and at this point are significantly lower than for the 120- and 60-day regimens

Thus, two methods appear to have promise in delaying the rate of emergence of resistant tubercle bacilli spacing the administration of streptomycin farther apart, and combining streptomycin with such an agent as PAS, which has tuberculostatic properties of its own

Although data were presented by individual investigators at the Seventh Streptomycin Conference, which indicate that rates of emergence of resistant strains of tubercle bacilli vary with the type of lesion which predominates in the

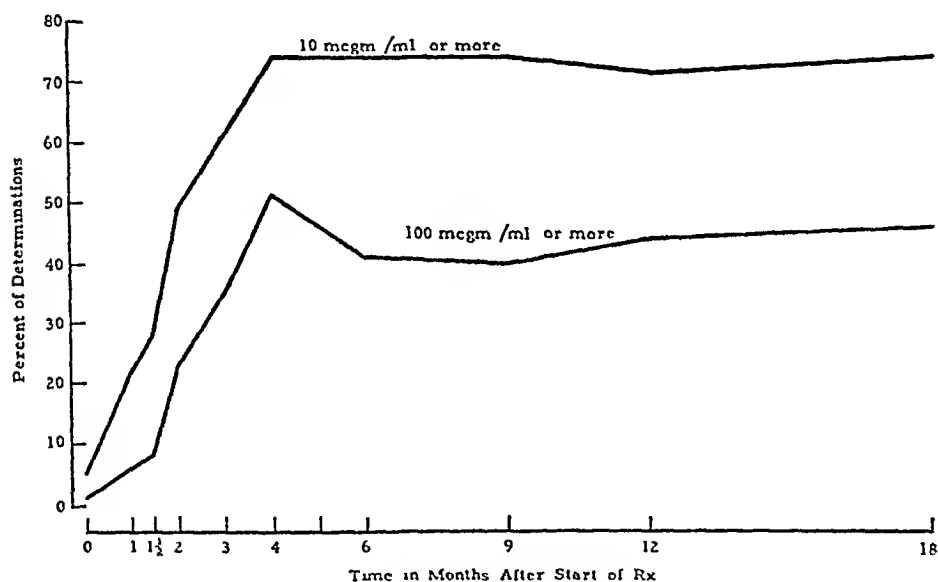


FIG 6 Percentage of organisms resistant to 10  $\gamma$  of streptomycin per ml or more and to 100  $\gamma$  of streptomycin per ml or more on 120 day regimens only

patient under treatment, it is not possible from the data reported to make this type of cross-tabulation until individual case reports are analyzed. It is probable, however, that the samples of cases reported for the different regimens do not differ appreciably with respect to such associated variables.

#### CLINICAL MATERIAL

Until analysis of cases reported on individual case report forms is complete, it is not possible to define with exactitude the composition of the clinical material treated with streptomycin as regards race, sex, and age. For the Seventh Streptomycin Conference (7) data are available for the nearly 1,500 cases of pulmonary tuberculosis most recently treated, which may be representative of the larger series. Seventy-four per cent were white, 23 per cent, Negro, and 3 per cent,

"other" or unknown Eighty per cent were reported as aged 50 or under and 20 per cent were over 50 years of age A very small number, probably less than 2 per cent, are female

The remainder of this report will be concerned chiefly with an examination of results obtained in the streptomycin therapy of pulmonary tuberculosis It is based on data from approximately 2,000 cases which were observed for at least 120 days after the start of therapy, and were treated on seven different regimens For this purpose the two 1 0 Gm a day for 120-day regimens (employing 5 and 2 injections a day, respectively) have been combined, as results between the two subgroups appear to be identical

### *Characteristics of Cases of Pulmonary Tuberculosis*

It is desirable to determine as accurately as possible whether the cases treated on the different regimens are comparable Greater assurance of comparability would have been available had more complete random selection been carried out Examination will be made of the following characteristics of cases of pulmonary tuberculosis at the start of treatment, on which data have been recorded stage of the disease, course of the disease during a pre-streptomycin observation period of two or three months, cavities demonstrable, and the predominance of exudation, as judged by the individual investigators The results are presented in figures 7 and 8

As shown in figure 7, the percentage of cases with far advanced disease at the start of treatment varied among the seven streptomycin regimens from 67.1 to 78.4 The percentage of cases with moderately advanced disease varied from 19.7 to 28.2, and of those with minimal disease from 0 to 5.4 per cent Whereas there is not more than a 10 per cent difference between the stages of the disease among the cases treated on these regimens, certain differences are statistically significant The lesions of the cases treated on the first three regimens employed 2/120<sup>6</sup>, 2/60, and 1/120 were significantly less far advanced (68 per cent average) than those treated on the four streptomycin regimens more recently studied, *i e*, 0.5/120, 1/42, 0.5/42, and 1 q 3 d /120 (77 per cent far advanced) Cases treated on the 1/42 regimen were reported as far advanced significantly more frequently than those on the 0.5/42 regimen

With respect to the percentages of cases with disease progressive prior to streptomycin therapy (figure 7), there is seen to be considerable uniformity (79 per cent) among the cases treated on four regimens 1/120, 2/60, 0.5/120, and 1/42 The lesions in the cases treated on the 0.5/42 regimen were less progressive (73 per cent), however, and on the 2/120 and 1 q 3 d /120 regimens were least progressive (67 per cent) The latter differences are statistically significant

In figure 8 are illustrated the values for the percentages of patients with cavernous disease and those whose disease was judged to be predominantly (more than 50 per cent) exudative With respect to the latter characteristic, the range of

<sup>6</sup> Numerator of fraction indicates daily dose of streptomycin in grams, denominator indicates duration of therapy in days The abbreviation q 3 d is used to designate "every three days"

variation of percentage of cases on different regimens is 14 per cent (from 59 to 73 per cent), with the exception of the cases treated on the 1 q 3d /120 regimen. The lesions in the latter group were far less predominantly exudative (24 per cent) than those treated on the other regimens. Significant differences also were found between cases treated on the 2/120 and 1/120 regimens, between those

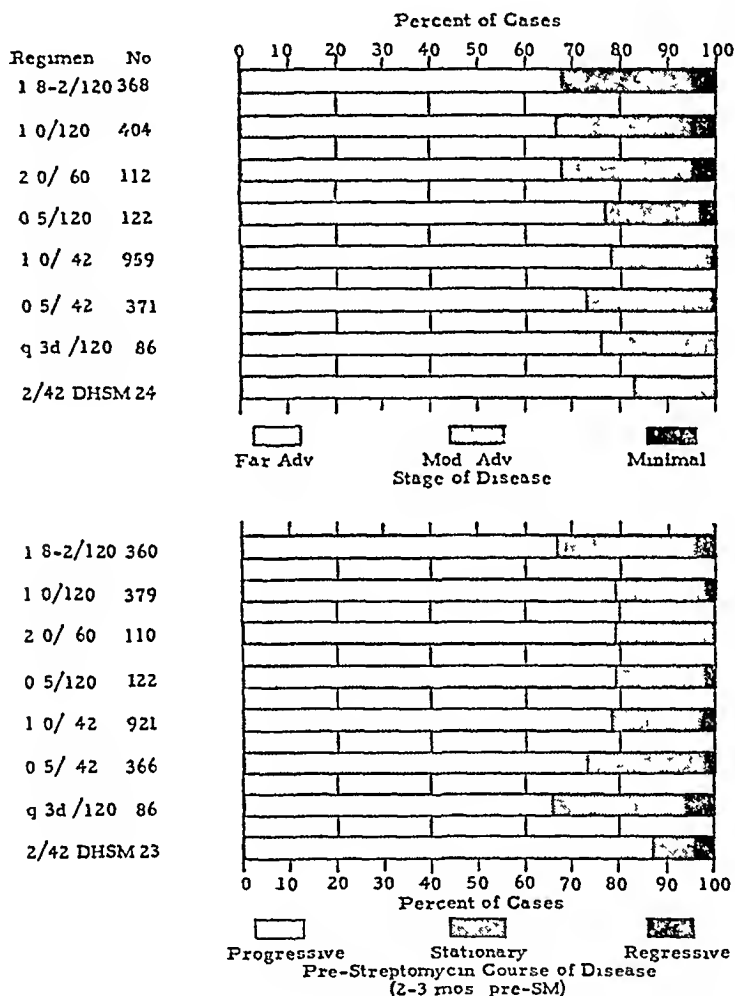


FIG 7 Characteristics of cases of pulmonary tuberculosis treated with streptomycin (at beginning of treatment)

treated on the 0 5/120 and 0 5/42 regimens, and between those treated on the 0 5/42 and 1/42 regimens.

A peculiar situation exists with respect to the percentage of cases reported as being demonstrably cavernous (figure 8). In gathering the data for the Seventh Conference on cases treated by the last four regimens, the investigators were asked to report whether cavities were small, medium, or large in size. For pre-

vious Conferences, on cases treated by the first four regimens, information only with respect to the presence or absence of cavities was requested and recorded. As figure 8 indicates, with the two different methods of reporting, the cases treated on the last four regimens are reported to have a significantly higher percentage of cavities. If, however, the data from the Seventh Streptomycin Con-

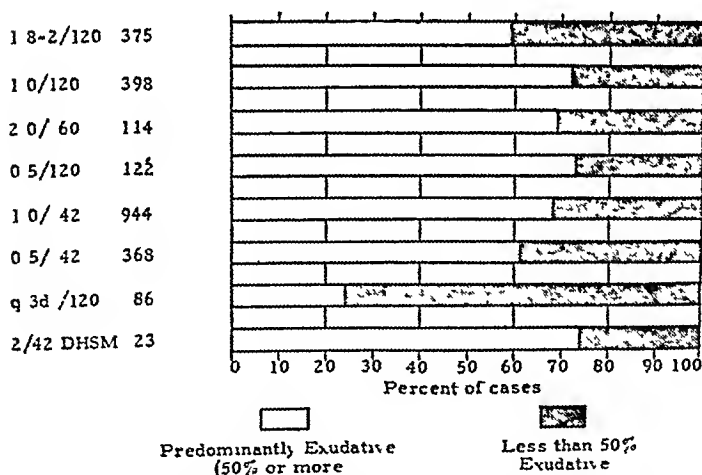
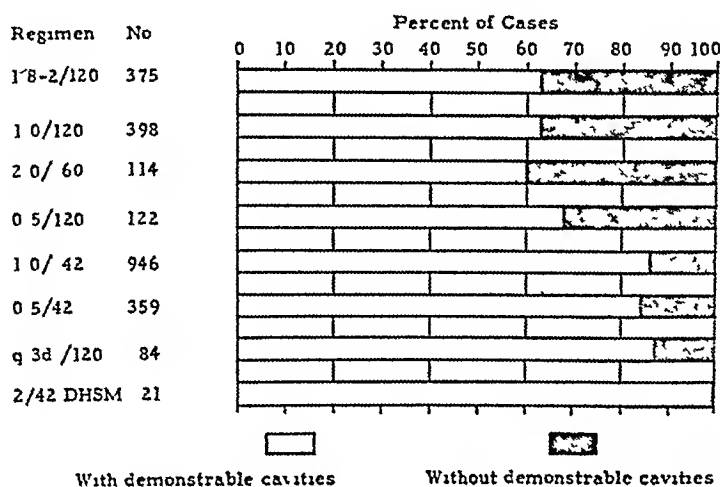


FIG. 8. Characteristics of cases of pulmonary tuberculosis treated with streptomycin (at beginning of treatment)

ference are re-examined and the cases treated on these four regimens which are reported as having small cavities are excluded, the percentages of cases reported as having *medium* or *large* cavities are not significantly different from those which were reported as cavernous on the first four regimens. The figures for per cent cavernous with this modification are given in table 3.

In summarizing the comparisons among the cases treated on the various regi-

mens with respect to stage, pre-streptomycin course, per cent cavernous, and per cent predominantly exudative, it is seen that a considerable degree of uniformity exists. Where differences have been indicated as being statistically significant, they have not been large in terms of percentages and the probability of the differences being significant has not been much less than 0.05.

Only one major difference has been noted: the cases treated on the 1 g 3d/120 regimen are much less predominantly exudative than those treated on the other regimens. In addition, the disease of the 2/120 cases was slightly less far advanced and less predominantly exudative than the lesions in those treated on the other regimens, and the disease in the 0.5/42 cases was slightly less far advanced, less progressive (pre-streptomycin) and less predominantly exudative than the 1/42 cases. Although included in figures 7 and 8, data on the characteristics of the 24

TABLE 3

*Characteristics of Cases of Pulmonary Tuberculosis Cases Reported as Cavernous, with Modifications†*

STREPTOMYCIN REGIMEN	NUMBER CASES REPORTED	TOTAL CAVITIES DEMONSTRABLE		NUMBER CASES REPORTED	LARGE AND ME- DIUM CAVITIES DEMONSTRABLE†	
		Num- ber	Per cent		Num- ber	Per cent
2 Gm /day—120 days <sup>5*</sup>	375	235	62.6			
1 Gm /day—120 days <sup>5</sup>	387	253	65.4			
2 Gm /day—60 days <sup>5</sup>	114	68	59.6			
0.5 Gm /day—120 days <sup>6</sup>	122	83	68.0			
1 Gm /day—42 days <sup>7</sup>	(946)	815	86.2	946	626	66.2
0.5 Gm /day—42 days <sup>7</sup>	(359)	300	83.6	359	228	63.5
1-2 Gm q 3d—120 days <sup>7</sup>	(84)	73	86.9	84	64	76.2
2 Gm /day—42 days <i>DHSM</i> <sup>7</sup>	(21)	21	100.0	21	16	76.2

\* Superscript numerals indicate Streptomycin Conference from *Minutes* of which data are obtained.

† See text for explanation. These data available only for regimens reported to the Seventh Streptomycin Conference.

cases treated with dihydrostreptomycin have not been discussed in detail. In thus stressing the similarity of the cases treated on the different regimens, the assumption has been made, according to the preceding paragraph, that cases on all regimens are comparable with respect to the incidence of cavernous disease.

It is advisable, in attempting to assess the therapeutic effect of streptomycin therapy of different regimens on the groups of cases so differentiated, to keep these differences in mind. But, until correlations or cross-tabulations are available from individual case report analyses, it will be difficult to determine the extent of allowance which should be made on their account.

From data gathered for the Seventh Streptomycin Conference (7), however, in the case of the 42-day regimens, it is possible to draw certain tentative conclusions. The lesions of the more predominantly exudative cases improve more than those lesions which were judged to be less than 50 per cent exudative. Moderately



advanced lesions improve more frequently than do far advanced lesions, and the improvement is more maintained (from the 42-day point to the 120-day point). Lesions which are stationary during the pre-streptomycin observation period improve least at 12 days, but slightly more than those which are progressive before streptomycin at 120 days. Those lesions, relatively few in number, which were regressive prior to streptomycin therapy improved most frequently at both the 12-day and the 120-day point.

### *Results of Treatment of Pulmonary Tuberculosis*

Examination will be made of the differences reported between cases of pulmonary tuberculosis treated on seven different streptomycin regimens in the following five respects: (1) change in certain clinical signs, (2) change in pulmonary lesions as determined by roentgenographic observation 120 days after the beginning of therapy, (3) incidence of relapse in pulmonary lesions, interpreted as worsening by roentgenographic observation after an initial improvement, (4) rates of "sputum conversion" by culture, and (5) mortality.

*Change in clinical signs.* Data have been collected on cases treated on eight regimens with respect to reduction of fever present at the start of therapy and weight change. Moreover, for the first three regimens explored, changes in sputum volume were recorded. The collected figures for these data are presented in table 4.

Approximately 40 per cent of patients treated on all regimens were reported as being not febrile at the time therapy was begun. In the remaining 60 per cent, febrile at the start of therapy, fever was reported as being not reduced in about one-eighth, as being reduced, but not to normal, in about one-third, and as being reduced to normal in slightly over one-half.

With respect to weight changes during the 120-day therapeutic period, the reported experience has been that 709 (38 per cent) of the 1,867 patients have had a weight gain of over 10 pounds, 68 (4 per cent) have had a weight loss greater than 10 pounds, and 1,090 patients (58 per cent) have had a weight change of between 10 pounds gain and 10 pounds loss, at the 120-day point.

Among the patients on the three regimens for which decrease in sputum volume is reported (and the amount of decrease is not known), the incidence of decrease is considerably less for those on the 60-day regimen than for those on the 120-day regimens.

*Change in roentgenographic observation at 120 days.* In figure 9 are shown the results of the investigators' ratings of roentgenographic change for the results of treatment on seven streptomycin regimens. In this figure are represented the percentage of cases in which the disease improved and those reported as exhibiting marked improvement.

Almost identical percentages of improvement of all degrees occurred with the first four regimens (2/120, 2/60, 1/120, and 0.5/120), averaging approximately 80 per cent. Improvement was noted in 75 per cent of the cases on the regimen

\* Numerator of fraction indicates daily dose of streptomycin in grams, denominator indicates duration of therapy in days.

TABLE 4

*Clinical Changes in Cases of Pulmonary Tuberculosis Treated with Streptomycin on Various Regimens during 120-day Treatment Period*

CLINICAL OBSERVATION	STREPTOMYCIN REGIMENS											
	2 Gm /day 120 days 5*			1 Gm /day 120 days 5*			2 Gm /day 60 days 5*			0.5 Gm /day 120 days 6*		
	Febrile Beg Rx		All Cases	Febrile Beg Rx		All Cases	Febrile Beg Rx		All Cases	Febrile Beg Rx		All Cases
	No	%	%	No	%	%	No	%	%	No	%	%
<i>Temperature during Therapy</i>												
Reduced to normal	135	58		166	64		16	40		37	51	
Reduced but not to normal	61	26		67	25		14	35		20	28	
Not reduced	37	16		28	11		10	25		15	21	
Tot Temp Elev Beg Rx	233	100	62	261	100	66	40	100	51	72	100	59
Temp not Elev Beg Rx	142		38	137		34	39		49	50		41
All Cases Treated	375		100	398		100	79		100	122		100
	No	%		No	%		No	%		No	%	
<i>Wt During 120-d Period</i>												
Wt gain over 10 lbs	155	41		179	45		17	21		50	41	
Wt change between gain 10 lbs and loss 10 lbs	204	54		198	50		55	70		67	55	
Wt loss over 10 lbs	16	5		21	5		7	9		5	4	
All Cases Treated	375	100		398	100		79	100		122	100	
<i>Change in Sputum Volume</i>												
Decreased in volume	266	71		295	74		34	43		†	†	
Not decreased in volume	109	29		103	26		45	57		†	†	
All Cases Treated	375	100		398	100		79	100		122	100	

CLINICAL OBSERVATION	STREPTOMYCIN REGIMENS											
	1 Gm /day 42 days 7*			0.5 Gm /day 42 days 7*			1-2 Gm q 3d 120 days 7*			2 Gm DHSM†/d 42 days 7*		
	Febrile Beg Rx		All Cases	Febrile Beg Rx		All Cases	Febrile Beg Rx		All Cases	Febrile Beg Rx		All Cases
	No	%	%	No	%	%	No	%	%	No	%	%
<i>Temperature During Therapy</i>												
Reduced to normal	346	54		101	46		29	74		5	33	
Reduced but not to normal	235	36		85	38		7	18		10	67	
Not reduced	66	10		36	16		3	8		0	0	
Tot Temp Elev Beg Rx	647	100	67	222	100	59	39	100	45	15	100	63
Normal or Unknown Beg Rx	315		33	152		41	47		55	9		37
All Cases Treated	962		100	374		100	86		100	24		100

TABLE 4—*Concluded*

CLINICAL OBSERVATION	STREPTOMYCIN REGIMENS							
	1 Gm /day 42 days †		0.5 Gm /day 42 days †		1-2 Gm q 3d 120 days †		2 Gm DHSM†/d 42 days †	
	No	%	No	%	No	%	No	%
<i>Wt During 120-d Period</i>								
Wt gain over 10 lbs	202	35	80	33	26	33	0	0
Wt change between gain 10 lbs and loss 10 lbs	358	63	155	65	51	65	2	100
Wt loss over 10 lbs	12	2	6	2	1	2	0	0
All Cases Treated	572	100	241	100	78	100	2	100

\* Numerals designate number of Streptomycin Conference from *Minutes* of which data are obtained

† Data on changes in sputum volume available only for first three regimens, reported in *Minutes* of Fifth Streptomycin Conference

† DHSM = Dihydrostreptomycin

employing 1.0 Gm a day every 3 days for 120 days, in 70 per cent of those on 1.0 Gm a day every day for 42 days, and in 60 per cent of the cases treated with 0.5 Gm a day for 42 days. Only the results on the last named three regimens are statistically significantly different, both from the first four regimens mentioned and among each other, with respect to all improvement of pulmonary lesions by roentgenographic observation between the start of treatment and 120 days thereafter. Table 5 presents the data of figure 9 as to the percentages of all improvement by roentgenographic observation, arranged according to the two variables in the regimens. The daily dose of streptomycin is presented in the horizontal axis, and the duration of therapy in the vertical.

If the reports of change on roentgenographic observation indicated as moderate improvement and marked improvement (including very marked improvement) are analyzed in a similar manner, however, a number of differences between regimens are found to be significant (table 6). Moderate and marked improvement is more frequent on the 2/120 regimen (66 per cent) than on the 2/60 regimen (52 per cent), on the 1/120 regimen (64 per cent) than on the 1/42 regimen (47 per cent), on the 0.5/120 regimen (57 per cent) than on the 0.5/42 regimen (41 per cent), on the 1/120 regimen (64 per cent) than on the 0.5/120 regimen (57 per cent), on the 2/60 regimen (52 per cent) than on the 1/42 regimen (47 per cent), and on the last named regimen than on the 0.5/42 regimen (41 per cent). Significant differences were lacking only between the following regimens: 2/120 and 1/120, and 0.5/120 and 1 q 3 d/120.

Referring to the preceding section on the relative roentgenographic improvement which could be anticipated from the differences in the characteristics of the disease, it will be observed that the 2/120 cases had the highest incidence of marked and moderate improvement (66 per cent), in spite of characteristics leading to the anticipation of relatively less improvement. Moreover, the cases

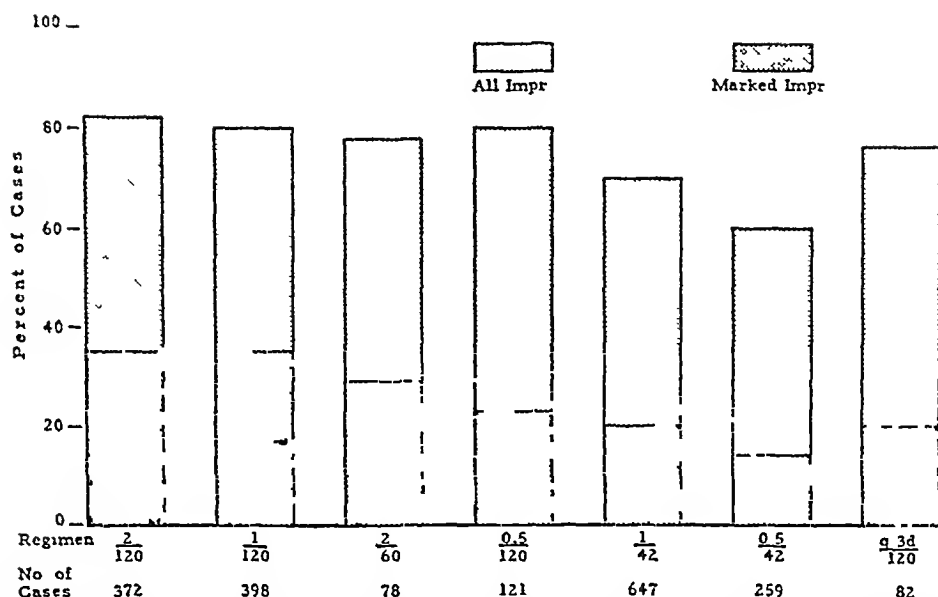


FIG 9 Percentage of improvement by roentgenographic observation in cases of pulmonary tuberculosis treated with streptomycin on various regimens (all observations 120 days after start of therapy)

TABLE 5

*Comparison of Roentgenographic Improvement at 120 Days among Seven Streptomycin Regimens in the Treatment of Pulmonary Tuberculosis*

DURATION OF TREATMENT, DAYS	DAILY DOSE STREPTOMYCIN, GM			
	2	1	$\frac{1}{2}$	q 3d
(Per cent of Cases)				
120	82	- 80	- 80	- 76
		*	*	
60/42	79	- 70	* 60	-

\* Difference between adjacent pairs statistically significant

- Difference between pairs not statistically significant

TABLE 6

*Comparison of Marked and Moderate Improvement by Roentgenographic Observation at 120 Days among Seven Streptomycin Regimens in the Treatment of Pulmonary Tuberculosis*

DURATION OF TREATMENT, DAYS	DAILY DOSE STREPTOMYCIN, GM			
	2	1	$\frac{1}{2}$	q 3d
(Per cent of Cases)				
120	66	- 64	* 57	- 49
	*	*	*	
60/42	52	* 47	* 41	-

\* Difference between adjacent pairs statistically significant

- Difference between pairs not statistically significant

treated on the 1/42 and 0.5/12 regimens, with characteristics leading to the anticipation of relatively more improvement, actually had the lowest. This was most marked in the 0.5/42 cases.

These results are again illustrated, in a three-dimensional manner, in figure 10. From these data the following patterns begin to emerge:

a Among the four 120-day regimens, there is only a slight decrease in the percentage of "all" improvement by roentgenographic observation as the daily dose of streptomycin is successively decreased from 2.0 Gm to 1.0 Gm to 0.5 Gm, and then to 1.0 Gm every three days, no one of the differences is statistically significant.

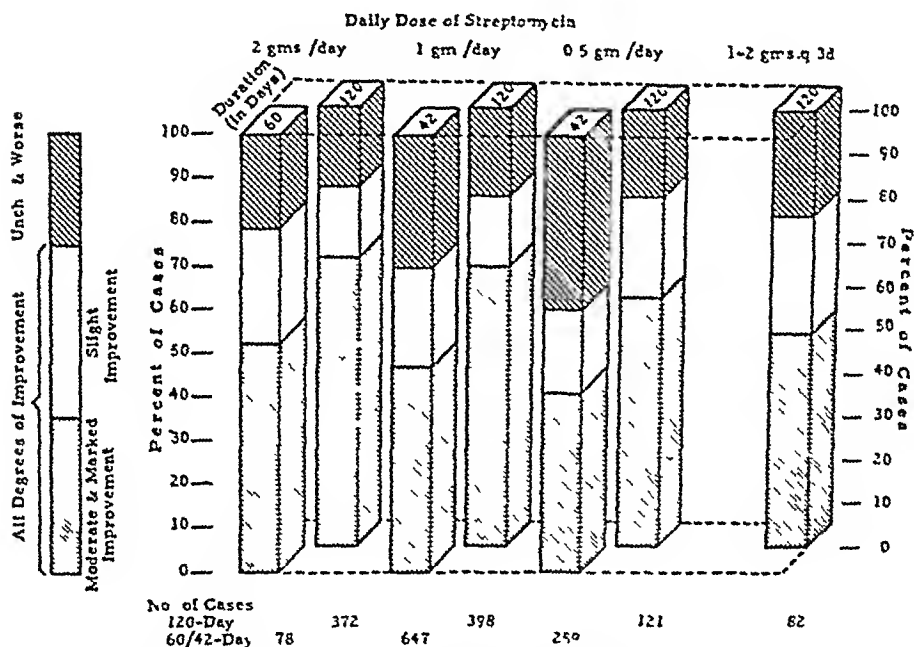


FIG. 10. Comparison of improvement in differing degrees by roentgenographic observation among seven streptomycin regimens in the treatment of pulmonary tuberculosis, according to daily dose and duration of therapy.

b Among the same four regimens, there is more decrease with respect to the incidence of "marked and moderate" improvement with decrease in daily dosage, although the differences are statistically significant only between the 1/120 and 0.5/120 cases.

c Among the three regimens of less than 120 days' duration, there is significantly less improvement (of "marked and moderate" degree) on the two 42-day regimens than on the 2/60 regimen, and, on regimens of 42-day duration there is significantly less improvement of "any" degree or of "marked and moderate" degree when the daily dose is decreased from 1.0 to 0.5 Gm a day. With these regimens of shorter duration, the effect of decreasing daily dosage of streptomycin appears to be more marked than in the case of regimens of 120 days' duration.

d When regimens of identical daily dosage are compared, there is in every instance a significant decrease in the per cent of cases reported as "markedly and moderately" improved as duration is decreased from 120 days to 60 or 42 days, and, in addition, a significant decrease for both the 1.0 Gm per day and the 0.5 Gm per day comparisons for "all" degrees of roentgenographic improvement as duration is shortened from 120 to 42 days

*1948 jury review* A brief word may be added concerning the roentgenographic changes found by a "jury" which in March 1948 (5) conducted a review of pulmonary tuberculosis cases treated on three streptomycin regimens

There was no statistical difference between improvement in any degree or any combination of degrees at the 120-day point among cases treated on the three regimens reviewed: 2.0 Gm per day for 120 days, 2.0 Gm per day for 60 days, and 1.0 Gm per day for 120 days

The mechanics of the jury review made it possible to make comparisons both at 60 days and at 120 days after the start of streptomycin therapy. Comparison of results at the 60-day point between the two 2.0 Gm per day regimens, both therefore treated identically up to this point, indicated that in all probability the cases selected for treatment on the 2.0 Gm per day for 120-day regimen differed significantly from those selected for treatment on the 2.0 Gm per day for 60-day regimen. For there was significantly less improvement in the former cases

The jury review indicated that at 60 days treatment with 2.0 Gm per day is superior to that with 1.0 Gm per day, for the differences at this point in time between these two regimens are statistically significant for all degrees of improvement. As the report of this jury review points out, however (5), the least amount of improvement occurs with the 2.0 Gm per day for 60-day regimen between the 60-day point and the 120-day point, so that the percentages of improvement at 120 days between the two regimens are not significantly different. If further observation and analysis substantiate this conclusion, it might be concluded that larger doses for shorter periods of time lead to results equal to those of smaller doses for longer periods of time, in the range of the variables covered by the jury review

*Relapse rates by roentgenographic observation* Figure 11 gives the rates for relapse by roentgenographic observation, defined as worsening after initial improvement, for cases treated on the seven streptomycin regimens. A considerable uniformity of rate of relapse as a function of time is reflected by these figures, especially for the 2/120<sup>8</sup>, the 2/60, the 1/120, and the 1 q 3d /120 regimens. Differences between these rates are not statistically significant. In figure 11 only one curve is used to depict the relapse rates for both 42-day regimens as they are practically identical. The relapse rates for these two regimens, and for the 0.5 Gm per day for 120-day regimen, are in all probability significantly higher than for the other regimens, although the possibility of differences in reporting must always be taken into account. When results from individual case report forms are available, and it is possible to be more certain of the accuracy of these observations

<sup>8</sup> Numerator of fraction indicates daily dose of streptomycin in grams, denominator indicates duration of therapy in days

than in such summary reporting as has been in use, it is quite possible that a just basis will be provided for the reserve with which investigators have employed the regimens of these lower total dosages.

*"Sputum conversion"* Figure 12 gives the data for "sputum conversion" by culture. The criterion for conversion was "negative sputum" and/or gastric cultures for a minimum period of three months. There is again a considerable uniformity in this regard among the cases treated on the different regimens. Until individual case analysis data are available, it has not been felt worth while to subject these data to statistical analysis.

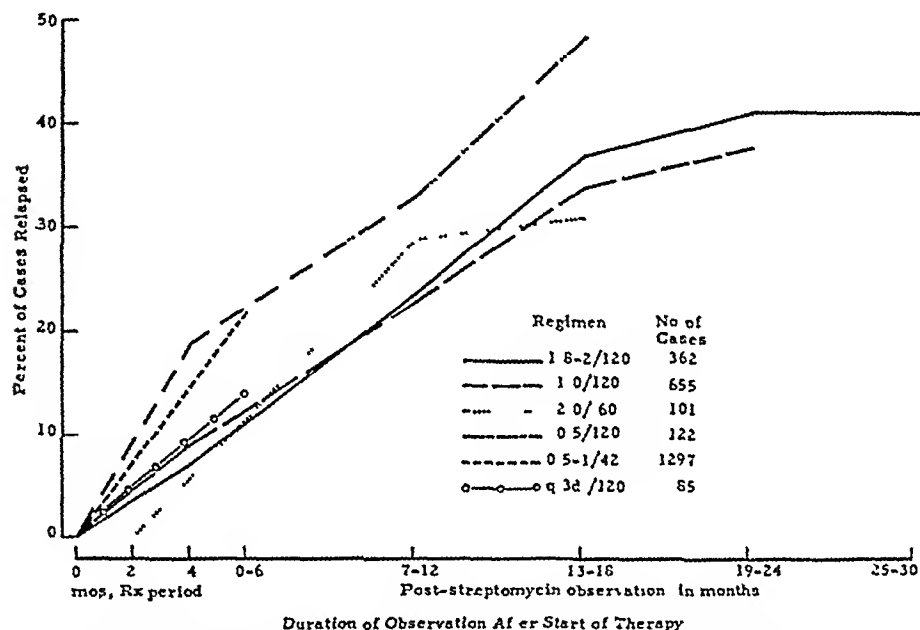


FIG 11 Rates of relapse (worsening after improvement) by roentgenographic observation in streptomycin-treated cases of pulmonary tuberculosis (according to regimen and duration of observation).

Table 7 may be studied in conjunction with figure 12, for it gives the frequencies with which collapse therapy is reported as having been used on the different regimens at different points in time. Data on the various types of collapse employed are not available. In general, less collapse therapy was employed in the earlier regimens, and the apparently higher "sputum conversion" rates noted for the two 42-day regimens (top curve in figure 12) may well be more related to the higher frequency with which collapse was employed in these cases than to the streptomycin therapy. Much more thorough analysis will be required to clarify the relative effects of collapse therapy and of streptomycin therapy on "sputum conversion" rates.

*Mortality* Figure 13 gives the data for cumulative mortality rates. It is to be noted that the three lowest rates are those for the three regimens with the largest total dosages (2.0 Gm. per day for 120 days, 1.0 Gm. per day for 120 days,

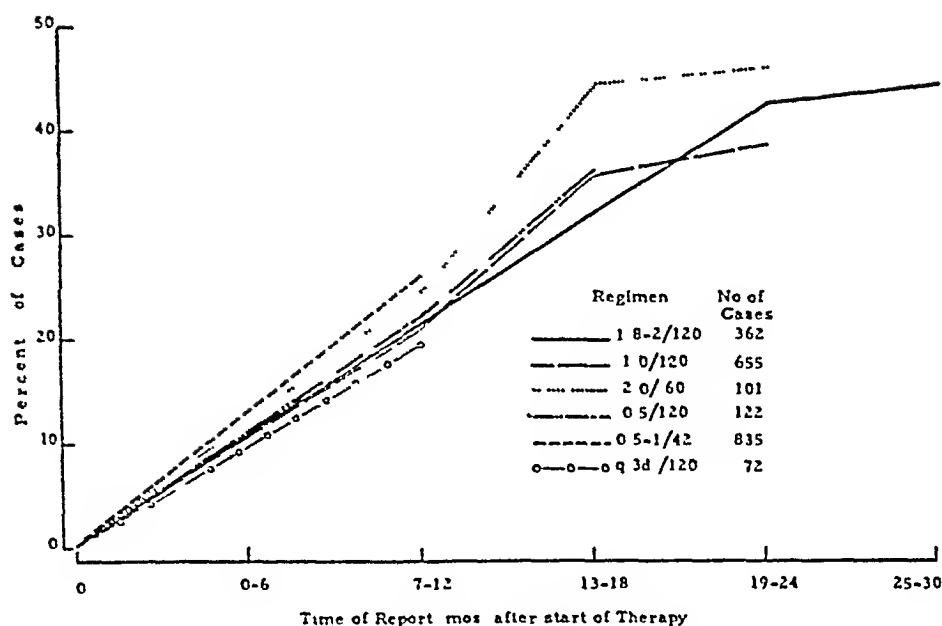


FIG 12 Rate of sputum conversion by culture in streptomycin-treated cases of pulmonary tuberculosis at various intervals after start of treatment (according to regimen)

TABLE 7

*Employment of Collapse Therapy in Patients with Pulmonary Tuberculosis Treated with Streptomycin on Various Regimens*

STREPTOMYCIN REGIMEN	DURING TREATMENT PERIOD (120 days)			TIME OF REPORT AFTER THE END OF TREATMENT											
				7-12 months			13-18 months			19-24 months			25-30 months		
	No Patients Followed	Collpsd		No Patients Followed	Collpsd		No Patients Followed	Collpsd		No Patients Followed	Collpsd		No Patients Followed	Collpsd	
		No	%		No	%		No	%		No	%		No	%
2 Gm /day—120 d	375*	12	3.2				375*	113	30.1	362*	157†	43.5	326†	155†	47.4
1 Gm /day—120 d	398*	45	11.3	398*	132	33.1	655*	299†	45.7	670†	358†	53.5			
2 Gm /day—60 d	114†	1	0.9	114*	39	34.2	101*	43†	47.4	122†	60†	49.3			
0.5 Gm /day—120 d	122*	6	4.9	122*	46	37.7	134†	60†	44.7						
1 Gm /day—42 d	691†	423	61.2												
0.5 Gm /day—42 d	251†	144	57.2												
1-2 Gm q 3 d for 120 days	83†	24	28.9												
Totals to date	2,064	655	31.3	634	217	34.2	1,265	526	41.6	1,154	575	49.9	326	155	47.4

\* Superscript numerals identify Streptomycin Conferences from *Minutes* of which data are obtained

† Data "during treatment period" for this regimen only for 60 days (not 120 days)

‡ Number of collapse cases calculated as follows: per cent collapsed during treatment (first column) added to per cent collapsed since end of treatment (from *Minutes* of Streptomycin Conferences) to give total per cent collapsed; this per cent applied to number of cases followed to give number of cases collapsed

and 2.0 Gm per day for 60 days) In figure 13 the mortality rates for the two 42-day regimens and that for the 0.5 Gm per day for 120-day cases are significantly higher than for the cases studied on the three earlier regimens



*Extrapulmonary Tuberculosis*

It would be desirable to analyze the effects of different streptomycin regimens on various tuberculous conditions in a manner similar to that in which cases of pulmonary tuberculosis have been analyzed. This is not possible in most instances for the two principal reasons that the number of cases of each condition treated on each regimen have been relatively small and the data defining the extrapulmonary conditions are less complete. It is therefore necessary to make certain assumptions, such as that cases treated on different regimens are roughly comparable in all important respects, and to interpret differences noted with greater reserve than in the case of pulmonary tuberculosis.

In a few tuberculous conditions treated with streptomycin, such as tuberculosis of the alimentary tract, tuberculosis of the pericardium, peritoneum,

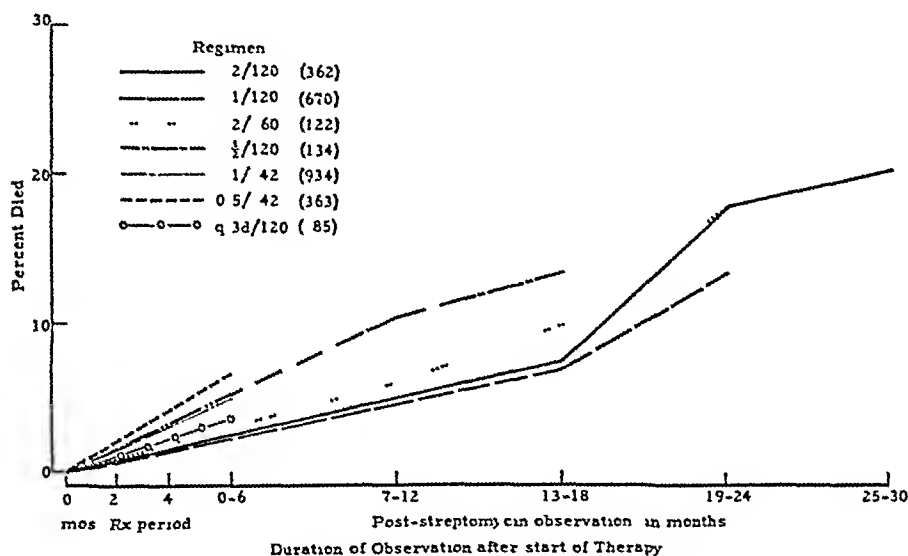


FIG 13 Mortality rates in streptomycin-treated cases of pulmonary tuberculosis, according to regimen and duration of observation

skin, eye, and ear, results have been reported to successive Streptomycin Conferences in summary form disregarding differences in results according to streptomycin regimen. In these conditions individualized types of analyses have been required. Streptomycin-treated cases of tuberculous enteritis (8) and of tuberculous peritonitis (9) have been so studied and reported, and studies are now under way in the instance of tuberculous pericarditis (10), tuberculous otitis media (11), tuberculosis of the skin (12), and of the eye (13).

*Tuberculous tracheobronchitis, laryngitis, lymphadenitis, and sinuses and fistulae.* Table 8 presents figures for the incidence of healing, improvement, absence of change, and worsening, in cases of tuberculous tracheobronchitis, laryngitis, sinuses and fistulae, and lymphadenitis, according to the streptomycin regimens employed.

TABLE 8

*Changes in other Tuberculous Lesions Treated on Various Streptomycin Regimens During Treatment Period (120 Days)*

TUBERCULOUS CONDITION	STREPTOMYCIN REGIMENS																All Cases (C-7*)	
	2 Gm /day 120 days (5)		1 Gm /day 120 days (5*)		1 Gm /day 42 days (7*)		0.5 Gm / day 42 days (7*)		0.5 Gm / day 120 days (6*)		0.2 Gm / day 120 days (6*)		0.2 Gm / day 42 days (7)					
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%		
<i>Tracheobronchitis</i>																		
Healed	31	46	32	71	40	67	20	51							123	59		
Improved	28	42	8	18	11	18	17	44							61	30		
Healed and Improved	59	88	40	89	51	85	37	95							184	89		
Unchanged	7	10	3	7	1	2	2	5							13	6		
Worse	1	2	1	2	0	0	0	0							2	1		
Unknown	0	0	1	2	8	13	0	0							9	4		
Total Cases	67	100	45	100	60	100	39	100							211	100		
<i>Laryngitis</i>																		
Healed	23	38	49	56	34	39	22	54	6	28					134	45		
Improved	28	46	32	36	21	24	14	34	13	62					108	35		
Healed and Improved	51	84	81	92	55	63	36	85	19	90					242	81		
Unchanged	5	8	2	2	22	25	3	7	0	0					32	11		
Worse	0	0	1	1	8	9	2	5	1	5					11	4		
Unknown	6	8	4	5	2	3	0	0	1	5					11	4		
Total Cases	61	100	88	100	87	100	41	100	21	100					297	100		
					(Fistulae only)		(Sinuses & retreatment)						(Sinuses & retreatment)					
<i>Sinuses and fistulae</i>																		
Healed	110	87	162	70	14	74	17	76	9	60	2	8	0	25	22	75		
Improved	10	8	35	23	3	16	3	14	7	47	1	33	2	20	62	40		
Healed and Improved	120	95	197	93	17	90	20	90	16	100	3	100	2	50	84	94		
Unchanged	5	4	10	7	1	5	1	5	0	0	0	0	0	0	22	5		
Worse	1	1	0	0	1	5	1	5	0	0	0	0	0	0	5	1		
Total Cases	125	100	207	100	19	100	22	100	16	100	3	100	2	100	111	100		
	2 and 1 Gm /day 120 days				(acute only)		(acute only)											
<i>Lymphadenitis</i>																		
Disappeared	12		0		0		0								12	25		
Improved	16		0		16		16								32	75		
Disappeared and Improved	28		0		16		16								48	100		
Unchanged	4		11		11		11								22	50		
Worse	2		0		0		0								2	5		
Total Cases	34		11		27		27								72	100		

\* % probably for patients who were not treated.

Examination of the figures in tuberculous tracheobronchial and laryngeal lesions during the 120-day treatment period reveals some inconsistencies, indicating that cases treated on different regimens may not have been entirely comparable, but they do reflect a generally favorable response of these conditions to streptomycin therapy in all variations of regimen investigated. Results in the treatment of tuberculous laryngitis appear slightly less satisfactory than in the treatment of tuberculous tracheobronchitis. Accurate data are not available with which to compare variations in therapeutic response with the type of lesion present at the start of treatment. When healing occurred, it did so, on the average, after six to eight weeks of therapy.

According to the figures in table 8, the response of both tuberculous sinuses and fistulae (the latter defined as communicating with a body cavity) to streptomycin therapy, with respect to per cent improved and healed, is uniformly excellent. With respect to the per cent healed (excluding those which merely improved), there may be a slightly less favorable response in cases treated on the regimens of smaller daily dosage. At the Seventh Streptomycin Conference a report was made from the Veterans Administration Hospital, Oteen, North Carolina (14), on results of treatment with 0.2 Gm. a day for 42 days. This analysis appeared to indicate that, on a daily dosage of this order, draining tuberculous sinuses respond less rapidly and less favorably to streptomycin than on regimens of larger daily dosage, and that 0.2 Gm. of streptomycin a day is at or near the lower level of therapeutic efficacy for this condition.

The data in table 8 for tuberculous lymphadenitis treated with streptomycin are relatively inconclusive, although it is suggested that the results of treatment with smaller doses for shorter periods of time are slightly inferior to those of treatment with larger doses for longer periods of time.

*Genitourinary tuberculosis.* A special study of cases of genitourinary tuberculosis treated with streptomycin has been made at the Veterans Administration Hospital, Bronx, N. Y. (15).<sup>\*</sup> Figures compiled for the Fifth, Sixth, and Seventh Streptomycin Conferences (5, 6, 7) suggest that there are no important differences according to streptomycin regimen (2.0 Gm. and 1.0 Gm. a day for 120 days, 1.0 Gm. and 0.5 Gm. a day for 42 days) for the following observations: disappearance and improvement of urinary symptoms, changes in pyelographic and cystoscopic observations, and changes in genital lesions. Improvement in urinary symptoms is reported in approximately 90 per cent of all treated cases, in cystoscopic observations in approximately 80 per cent, in genital lesions in approximately 50 per cent (in many instances associated with surgical procedures), and in pyelographic observations in approximately 25 per cent.

Figure 14 shows the "urinary conversion" rates by culture of 140 cases of genitourinary tuberculosis treated on three regimens, in all of which urines positive for tubercle bacilli were demonstrated at the start of treatment. According to this criterion of the results of streptomycin therapy, which is more objective

<sup>\*</sup> In this article the authors have made a detailed analysis of these streptomycin-treated genitourinary cases. The reader is referred to it for more careful assessment of the variables of treatment of genitourinary tuberculosis than is here possible.

and probably of more clinical significance than those referred to in the preceding paragraph, it is observed that a regimen of larger daily dosage and longer duration (2.0 Gm a day for 120 days) appears to exert a more favorable influence on the results. Probably because the numbers of cases treated on the different regimens are not large, the differences between the percentages of "urinary conversion" indicated are significant in only one instance. The percentage of cases with urine "converted" at 120 days after the start of treatment on the regimen of 2.0 Gm a day for 120 days (83 per cent of 65 cases) is significantly greater than the percentage of cases with urine "converted" on the regimen of 1.0 Gm a day for 42 days (55 per cent of 40 cases). Differences between the percentages

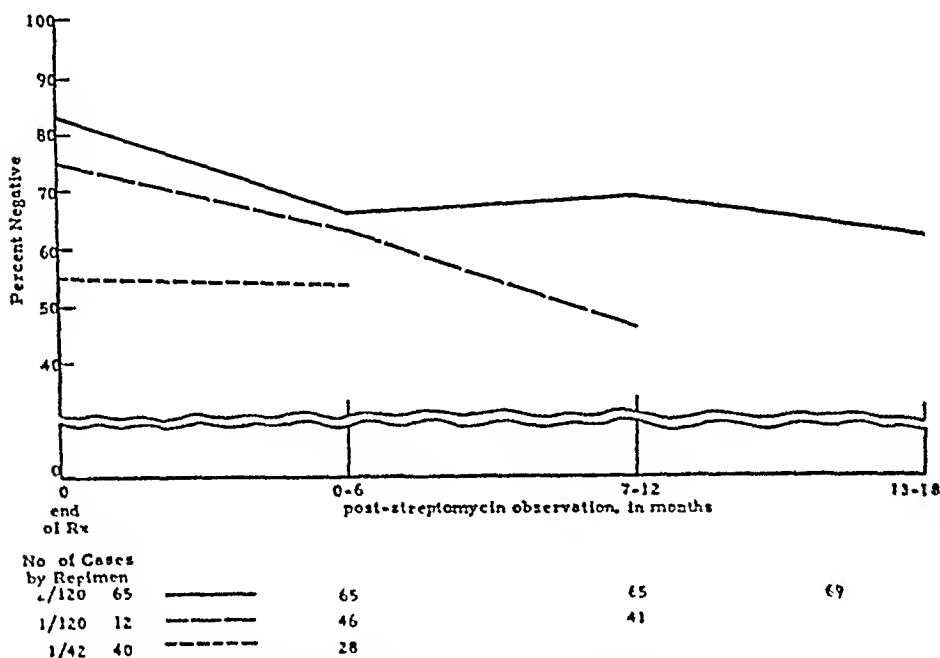


FIG. 14 Percentage of urines negative for tubercle bacilli by culture in streptomycin-treated patients with genitourinary tuberculosis during post treatment follow-up period

of "urinary conversion" during the follow-up period indicated in figure 14 are not significant in any instance.

**Tuberculosis of bone, joint, and cartilage.** In cases of tuberculosis of bone, joint and cartilage reported to the Fifth, Sixth and Seventh Streptomycin Conference (5, 6, 7), the cooperating investigators were reluctant to draw conclusions as to the significance of results obtained with the several regimens. A survey of approximately 100 cases conducted in March 1948 and previously reported (5), has therefore been relied upon to a considerable extent. It indicates that, before 6 per cent of the lesions were improving and 70 per cent had improved after 12 months of streptomycin therapy, 10 per cent of the lesions improved during the 12-month therapeutic period and 70 per cent showed improvement at the end of 12 months. The condition at the start of therapy, at the end of 12 months, and at the end of 24 months

period averaging 1 month (8 months from the start of therapy). It is planned that another review of such cases, with a longer follow-up period, will be carried out in the autumn of 1949.<sup>10</sup>

From the data gathered at the review of cases of tuberculosis of bone, joint, and cartilage conducted in March 1948 (16), additional analysis has indicated that results of streptomycin treatment in these conditions may be superior with 2.0 Gm a day to those with 1.0 Gm a day, and that longer duration of therapy (over 120 days) may be associated with a greater frequency of improvement by roentgenographic observation than shorter durations of therapy (under 120 days). Figures 15 and 16 present these data. Because the number of lesions reviewed was relatively small (105), statistical tests do not prove that the observed differ-

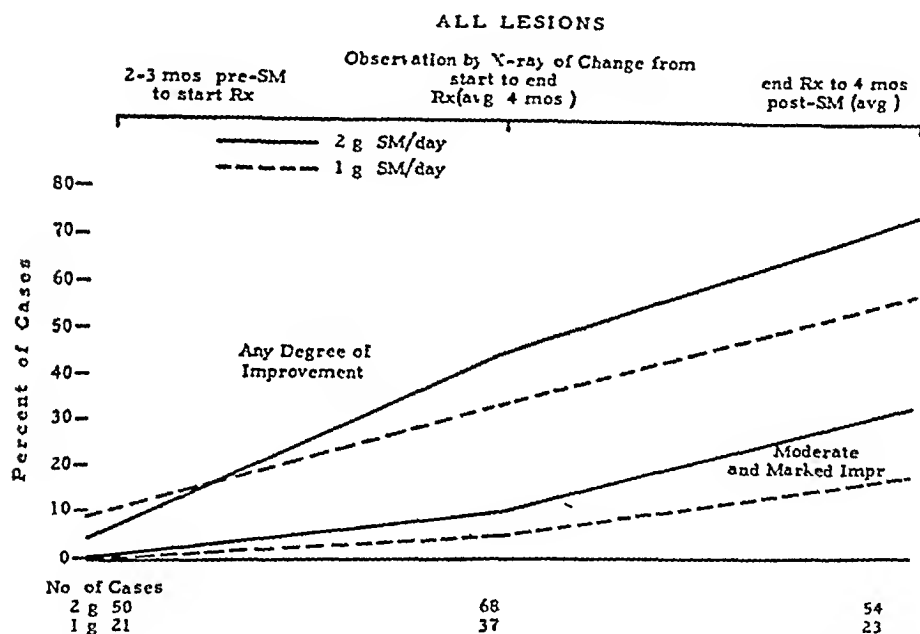


FIG 15 Effect of dosage on incident and rate of roentgenographic improvement of tuberculosis of bones and joints treated with streptomycin (1.0 to 2.0 Gm for 100 to 102 days in 85 per cent of cases). Review by Doctor Ghormley.

ences between the regimens are significant. If the trends noted continue in the larger series which is to be reviewed, however, the differences would acquire increasing statistical significance.

*Miliary tuberculosis and tuberculous meningitis.* Patients with miliary tuberculosis and tuberculous meningitis have been treated on a variety of therapeutic regimens. The majority of patients have received at least 2.0 Gm a day of streptomycin intramuscularly, and patients with tuberculous meningitis have received, in addition, 50 mg (originally 100 mg) of streptomycin intrathecally three times a week.

<sup>10</sup> This review was held September 17-18, 1949. The results will be published in the *Minutes of the Eighth Streptomycin Conference*, November 10-13, 1949, Atlanta, Georgia.

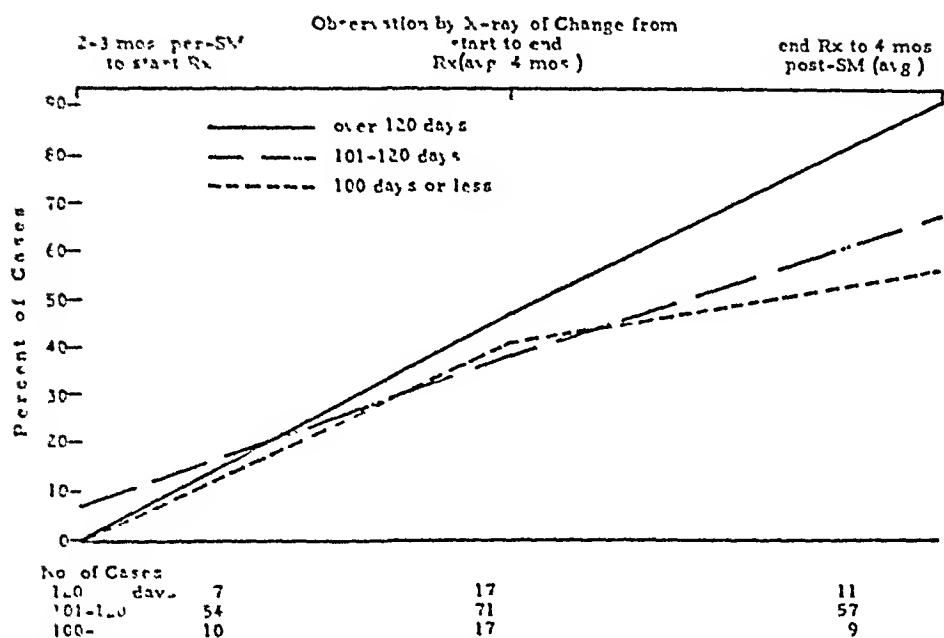


FIG 16 Effect of duration of therapy on rate of roentgenographic improvement of tuberculosis of bones and joints treated with streptomycin (all lesions (10 to 20 Gm for 100 to 120 days in 85 per cent of cases) Review by Doctor Ghormley

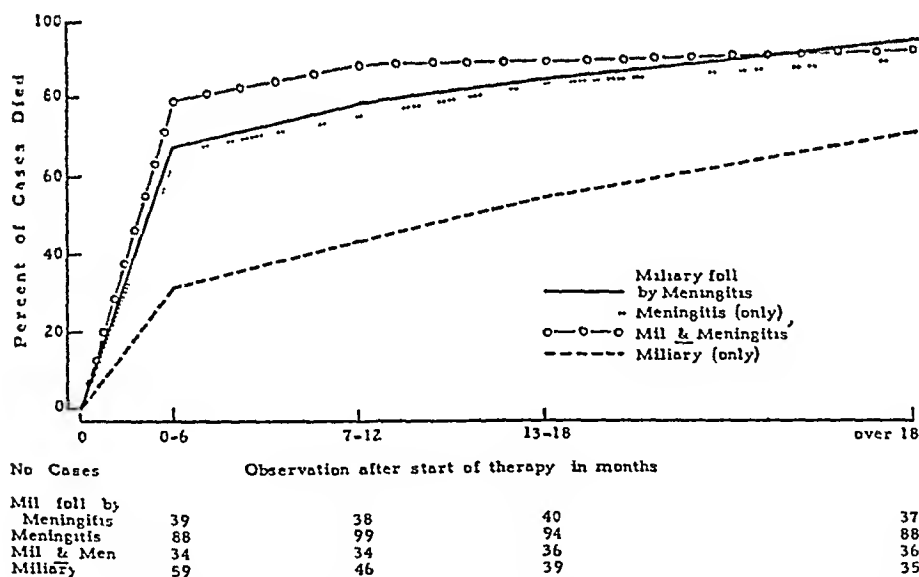


FIG 17 Cumulative mortality of cases of miliary tuberculosis and tuberculous meningitis treated with streptomycin, at various intervals after the start of therapy

An analysis of the first 100 cases treated has been made (17) and a follow-up of the same group was carried out in the spring of 1949 (18). Results of the 234 cases which have been treated and reported to date, presented only with respect to cumulative mortality, are given in figure 17.

With the increasing realization that comparatively favorable initial results are tempered by a steadily mounting death rate with the passage of time, usually because of the development of meningitis in patients who previously had acute miliary tuberculosis and relapses in those with meningitis, a number of variations of streptomycin therapy have been explored. These include interrupted therapy in various forms, the omission of intrathecal therapy, and the combined use of two or more antimicrobial drugs. Data permitting cross-tabulations of results are only available with respect to the latter, and these are presented in figure 18. The chief drug used in addition to streptomycin in this series has been Promin (sodium p,p'-diamino-diphenylsulfone-N,N'-didextrose sulfonate), given intra-

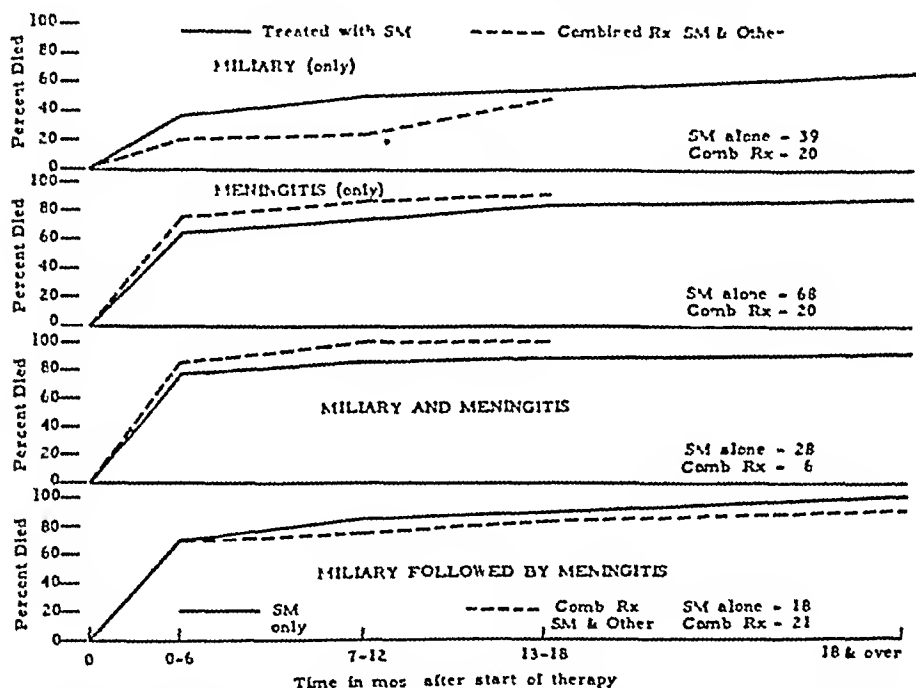


FIG 18 Mortality of cases of miliary and meningeal tuberculosis treated with streptomycin and combined therapy, at intervals after start of therapy

venously in a daily dosage of 4.0 Gm during two of every three weeks. Figure 18 does not suggest that such combined chemotherapy has improved the mortality experience in miliary and meningeal tuberculosis over that for treatment with streptomycin alone.

#### DISCUSSION

It has been the primary purpose of the cooperative investigation to explore in a systematic manner the effects of a relatively restricted number of variables in the treatment of tuberculosis. These have been particularly the variables of streptomycin regimens, of variations in dosage, and duration of therapy. Access through the cooperating Study Units to a relatively large volume of clinical

data, selected treated and reported under uniform conditions, has made it possible to gather in a short time data which are more significant than usually is possible without such a coordinated study.

In addition to the larger objectives of the study, within the framework of the larger investigation, individual cooperating investigators have the opportunity, and are in fact encouraged, to explore problems subsidiary to the larger problem. Such smaller investigations may have the disadvantage of smaller size, but have the advantages of more intensive and uniform examination of results than is possible in the study as a whole, and several such studies have pointed the way for the larger investigation at opportune moments.

*Evaluation of results in the treatment of tuberculosis* The problem of the evaluation of any form of therapy is not an easy one in so chronic and variable a disease as tuberculosis. It probably is not an unfair statement to say that no uniform or standard method of reporting results of treatment of any form of tuberculosis has been devised. There is not agreement as to which criteria are the most important or relatively most important. The usual appraisal is a composite of a number of clinical observations, such as roentgenographic change, sputum examination, clinical signs, and erythrocyte sedimentation rate. In the final analysis *survival without detectable reactivation of the disease under essentially "normal" socio-economic conditions* is the criterion for success of therapy. But obviously there are gradations of efficacy short of this end result which are recognized as satisfactory, and such a criterion, if solely relied upon, cannot be applied until many years have passed. There is serious need for accurate evaluation of all available clinical data at all stages of the treatment of the disease in order that as accurate prediction of later results may be made as possible and in order that new regimens of therapeutics may be evaluated with as much promptness and validity as possible.

The history of the cooperative streptomycin investigation of the Veterans Administration, Army, and Navy has been in large part a study of such difficulties of evaluation. Investigators have been under the opposed pressures of a natural desire to apply their results, premature as they may be, to clinical material, and of caution and patience in modifying regimens in the scientific interests of the study as a whole.

Conclusions drawn or inferred from data reported have in some instances differed from impressions and estimates of individual investigators and it has not been possible to disregard the latter entirely, for no sets of figures can completely represent clinical experience.

Results of streptomycin treatment of pulmonary tuberculosis have been presented with respect to such criteria as clinical signs, change by roentgenographic observation during the therapeutic period, relapse by roentgenographic observation during the post-streptomycin observation period, "sputum conversion" at various points in time, and the mortality experience to date. While it may be expected that there will be disagreement as to the relative clinical importance of these observations, a few relative weightings are increasingly apparent.

The initial optimism engendered by the prompt defervescence of patients with



acute forms of tuberculosis when streptomycin therapy is begun has been tempered by the realization that this initial response may generally be anticipated and still have little relationship to a reasonably satisfactory subsequent clinical course. To a lesser extent, the initially favorable roentgenographic response of pulmonary tuberculous lesions is likewise tempered by a steadily mounting percentage of relapse during and subsequent to streptomycin therapy.

Suppression of multiplication of tubercle bacilli in the body as a result of streptomycin therapy is reflected initially by "conversion" of sputum and urine, cessation of drainage from sinuses, et cetera, in a considerable percentage of cases. But it is probable that all tuberculous foci in the body are never eliminated with streptomycin therapy, and the reappearance of tubercle bacilli from the same sources likewise limits the significance of this initial response.

Such clinical responses to streptomycin must be interpreted in the light of known facts and many others need to be determined. The emergence of streptomycin-resistant strains of tubercle bacilli undoubtedly is one of the most important limiting factors in such chemotherapy. The demonstrated inability of streptomycin to have an appreciably favorable influence upon lesions with a large necrotic component is another. Undoubtedly tuberculous lesions of different tissues and organs respond to streptomycin therapy in dissimilar fashion for reasons not completely understood. Investigation is needed as to the role which other factors may play, such as those of age, race, degree of disability of the host, concomitance of multiple tuberculous lesions, and probably others as yet unsuspected.

In pulmonary tuberculosis there are indications that the less acute forms, those which might be termed subacute, respond approximately as well to streptomycin as do the acute, and that even in the chronic forms, for these are almost never devoid of some acute component, some improvement may occur. In the more chronic stages of the disease, however, relapse is more likely to occur than in the more acute stages and, when streptomycin is employed in chronic disease, it is of the utmost importance to combine it with other suitable procedures such as collapse and excisional therapy in a well-integrated therapeutic program. Additional investigations are needed to determine the optimal manner in which such combined therapy may be applied.

With so many unanswered problems remaining in the streptomycin treatment of tuberculosis, results of investigation such as those which have been presented must be regarded as preliminary, and restricted in their significance. Yet the study, through the conditions of its formation, has, it is believed, made possible certain conclusions of value, with respect to the relatively few variables on which it has concentrated.

*Statistical considerations* Hart (19) has said

It may be stated that careful objective clinical assessment, based on previous experience with similar types of cases as a standard, should, with rigid safeguards, be adequate to demonstrate whether a new drug gives either benefit or no benefit, provided its action is more than slight. On the other hand, the inclusion of a matched control series, studied concurrently in order to permit comparisons having statistical validity, would seem im-

perative for a precise evaluation of a new drug's possibilities, limitations, and the degree of permanence of its benefit

As has been pointed out the need for concurrent controls has been recognized in this study and there has been random selection of cases on the four streptomycin regimens studied since April 1948 and, before that, to a certain degree on the other streptomycin regimens except in the case of the first one employed, the regimen of 1.8 or 2.0 Gm a day for 120 days

Presentition of results has nevertheless indicated that the selection of cases for treatment on different streptomycin regimens has not entirely reached the levels which are scientifically desirable. In the case of pulmonary tuberculosis, with relatively large numbers of cases, a considerable uniformity of clinical material, nevertheless, is present, certainly to a greater extent than in the case of various forms of extrapulmonary tuberculosis which have been investigated in this study and in which relatively smaller series were available

The limitations of the methods of reporting results of the study to date have been mentioned. It is believed that, when detailed analysis of results is possible through the medium of the individual case report form recently initiated, many of the limitations of the data considered in this report will be removed and information along other important lines will be forthcoming. It is necessary at the present time to interpret the data which are available with the reservations indicated by these considerations

With the increased number of cases studied and the increasing complexity of the study in general, the necessity for statistical evaluation has increased. This is particularly apparent in comparisons of results of treatment by several regimens. In Hart's words, streptomycin is no longer a "new drug", differences in its effect according to regimen are not "more than slight", and it does seem desirable to attempt a "precise evaluation of possibilities, limitations, and the degree of permanence of its benefit"

*The "best" streptomycin regimen* It has not been the purpose of the study to define the single streptomycin regimen which is best suited to the treatment of all tuberculosis, or of any form of tuberculosis. This would be an obviously impossible and impractical undertaking at the present time. Emphasis has been placed on evaluation of such variations in streptomycin regimens as daily dose and duration of therapy

The results presented have indicated with considerable statistical validity that, with respect to certain clinical observations in both pulmonary and extrapulmonary tuberculosis, streptomycin therapy of longer duration is superior to that of shorter duration, and, moreover, to a lesser extent, that a daily dose of 2.0 Gm is superior to a daily dose of 1.0 Gm. In the latter instance, however, precise statistical analysis was required to detect this superiority, and the differences are slight even if statistically significant

Moreover, it cannot be too strongly emphasized that slightly superior clinical results are only one part of the problem. Data have been presented which indicate conclusively that a streptomycin regimen of 2.0 Gm a day is associated with much greater toxicity than one of 1.0 Gm a day, especially if therapy is long

continued. It is as yet premature to expect that dihydrostreptomycin, or other derivatives of streptomycin which may yet be developed, will prove to be the entire solution to this problem. And the data for the rates of emergence of resistant organisms indicate conclusively that streptomycin administered daily for long periods of time, up to three or four months, and not in combination with other tuberculostatic drugs, results in an unfortunately high percentage of drug-resistant microorganisms.

The demonstrated degree of superiority of streptomycin regimens of greater duration and higher daily dosages, according to clinical observations, therefore, is of more theoretical than practical importance if the present limitations of toxicity and drug resistance remain unchanged. From the theoretical standpoint, there may be merit nonetheless in the recognition of these differences. Should, for example, a new derivative of streptomycin be developed which is markedly less toxic than streptomycin (or dihydrostreptomycin) and identical in therapeutic effect, it is probable that administration with larger daily doses would be advisable. And should devices be found which definitely reduce the rate of emergence of streptomycin-resistant tubercle bacilli on continuous daily therapy, as may be the case with combined streptomycin-PAS therapy, it is probable that courses of longer duration would be desirable. Another regimen with indications of great promise of maintaining therapeutic efficacy and delaying the emergence of drug resistance is that of administering streptomycin at intervals of approximately three days. It is possible that these two variations in therapy, combined chemotherapy and interrupted therapy, may themselves be combined to effect still further reduction of the limitations of drug fastness, and these possibilities are currently being investigated within this cooperative program. If, through such devices, the emergence of resistant strains of tubercle bacilli were to be further delayed, it is possible that it will be found desirable appreciably to lengthen the duration of such combined chemotherapy.

Summarizing this discussion of the relative merits of different streptomycin regimens in the treatment of tuberculosis, it may be said that the difference in clinical response between treatment with 2.0 Gm a day and with 1.0 Gm a day is very slight and of more theoretical than practical importance, particularly in view of the definitely greater toxicity of a regimen employing 2.0 Gm a day. The difference in therapeutic response between treatment with 1.0 Gm a day and with 0.5 Gm a day is greater, the latter being definitely less effective, and there is not corresponding decrease in toxicity. In the light of these considerations *it is probable that 1.0 Gm a day is the dosage of choice* of the three daily dosages investigated, all factors being considered.

With respect to continuous daily streptomycin therapy, although regimens of 42-day duration are found to be associated with less therapeutic response than their longer counterparts with equivalent dosages because of the importance of the limitation of drug resistance, it is nevertheless probable that duration of continuous therapy should generally not exceed 42 or 60 days. Addition of PAS, and such other devices as spacing administration of streptomycin farther apart, may modify this statement. It has not yet been demonstrated conclusively,

however, to what extent modifications will definitely delay drug resistance and retain therapeutic equivalence. Toxicity is a readily observed deterrent to the use of larger daily doses. The emergence of resistant strains of tubercle bacilli is not easily detected and is no less serious a deterrent to unwise use of streptomycin. Until regimens of combined therapy, or "interrupted" therapy, or both, have been standardized, therefore, the determination of the duration of streptomycin therapy should always keep in mind the limitation of emerging resistance. Relatively short courses of streptomycin therapy, in the range of 42 and 60 days, duration, with therapeutic efficacy approximating that of longer courses but with definitely less associated drug resistance, therefore at the present time appear to be the ones most appropriate for general use with deviations therefrom for special purposes only.

#### SUMMARY

1 Between July 1946 and April 1949, the cooperative investigation of the Veterans Administration, Army, and Navy has studied the effects of streptomycin in the treatment of approximately 4,500 cases of tuberculosis, including nearly 2,000 cases of pulmonary tuberculosis. Careful planning and effective liaison have resulted in uniform selection of clinical material and recording of results.

2 The clinical effects of seven different streptomycin regimens have been investigated, primarily with respect to the toxicity of the antibiotic, the rate of emergence of resistant strains of *M. tuberculosis*, and the therapeutic result. In addition, dihydrostreptomycin has been studied since December 1948.

3 It has been demonstrated that reducing the daily dosage of streptomycin from 2.0 Gm. to 1.0 Gm. to 0.5 Gm. has successively reduced the incidence of all important toxic manifestations, and that reducing the duration of administration of the drug from 120 days to 60 or to 42 days likewise is associated with reduced toxicity. A reduction of the number of injections into which the total daily dosage is divided has also been associated with decreased incidence of toxicity. These observations have been applied to vestibular dysfunction, impairment of renal function, dermatitis, drug pyrexia, and other toxic manifestations discussed in the text. Dihydrostreptomycin has been studied in only 56 cases, but it appears that it is less toxic than streptomycin with respect to vestibular function, but not otherwise significantly different in toxicity from its parent nonhydrogenated substance.

4 Strains of tubercle bacilli resistant to 10  $\gamma$  per ml. or more of streptomycin emerge at a fairly regular rate, which appears to be independent of daily dosage in the ranges studied but definitely related to duration of therapy. At the end of 42 days of daily administration, approximately 35 per cent of specimens examined are resistant to 10  $\gamma$  per ml. or more, at the end of 60 days, 50 per cent, at the end of 120 days, 75 per cent. Administration of streptomycin every third day instead of daily results in rates of emergence of resistant strains of approximately one-third of these figures. Combined therapy, with para-aminosalicylic acid (PAS) added to streptomycin, reduces the rates of emergence of resistant strains still further.

5 Cases of pulmonary tuberculosis treated on seven streptomycin regimens, essentially homogeneous with respect to such criteria as stage of disease, pre-streptomycin course, and per cent cavernous and predominantly exudative, exhibited clinical results of considerable uniformity within the range of variables of regimen studied

(a) Fever, when present at the start of treatment, was reduced in seven-eighths of the patients and reduced to normal in slightly over half. Three-eighths of the cases had a weight gain of over 10 pounds. The variations by regimen in these respects are not large.

(b) Roentgenographic improvement varies from 82 per cent in cases treated with 2.0 Gm. a day for 120 days, to 60 per cent in cases treated with 0.5 Gm. a day for 12 days. Among cases treated for 120 days, there is little decrease in the percentage showing all degrees of improvement, as the daily dose is decreased from 2.0 Gm. to 1.0 Gm. to 0.5 Gm., and to 1.0 Gm. every three days. There is more decrease in the percentage reported as exhibiting degrees of roentgenographic improvement defined as "marked" and "moderate." There is a significant decrease in the percentage of cases classified as "markedly and moderately" improved in each daily dosage category (2.0, 1.0, and 0.5 Gm. a day) when the duration of therapy is reduced from 120 to 60 or 12 days.

(c) Relapse rates are quite uniform for cases treated with larger total dosages and are slightly higher for cases treated with 1.0 Gm. a day for 42 days, or 0.5 Gm. a day for 120 or 42 days.

(d) Rates of "sputum conversion" by culture are remarkably uniform on all regimens studied, in spite of a considerable variation in the incidence of collapse therapy which was employed in the different groups.

(e) Mortality experience has been uniform for the cases treated on the regimens of higher total dosages; it is slightly greater for the cases treated for 42 days, as well as those treated with 0.5 Gm. a day for 120 days.

6 It has not been possible in cases of extrapulmonary tuberculosis to study the results of variations in streptomycin therapy with the same thoroughness as in the case of pulmonary tuberculosis, because of smaller numbers of cases and less complete data. To the extent that such an analysis is possible, however, the same trends with respect to variables of regimen are observed in these cases as in pulmonary tuberculosis.

7 The experience of the investigation in the treatment of miliary and meningeal tuberculosis, including a number of additional variations in therapy, has been presented. Whereas approximately 30 per cent of cases of miliary tuberculosis survive 18 months or more after the start of therapy, 10 per cent or less of cases which have tuberculous meningitis, whether with or without miliary tuberculosis, survive 18 months or more.

8 Primary emphasis has been placed in this report on the effect of variations in streptomycin regimen. Recognition has been given the complexity of the problem of the evaluation of results, including the statistical and the clinical. The investigation has probably raised as many questions as it has answered, and it is evident that the evaluation of streptomycin therapy in tuberculosis calls for the



careful balancing of many separate factors, especially those of toxicity, drug resistance, and the various facets of clinical response

9 It is concluded that there has not yet been determined to be one "best" streptomycin regimen. One gram a day appears to be a satisfactory daily dosage, but the duration of therapy, the spacing of single administrations, and the combination with other chemotherapeutic agents with tuberculostatic properties such as PAS, have not yet been determined with validity. Because of the limitations imposed upon streptomycin therapy by the phenomenon of drug resistance, it is believed that duration of therapy should generally not exceed 42 or 60 days, until procedures designed for delaying the emergence of streptomycin-resistant strains of tubercle bacilli have been adequately standardized.

#### SUMARIO

*Justipreciación de los Régimenes de Estreptomicina en el Tratamiento de la Tuberculosis. Reseña del Estudio Realizado por la Administración de Veteranos, el Ejército y la Marina de los E U A*

1 Entre julio, 1946 y abril, 1947, en una investigación cooperativa por la Administración de Veteranos, el Ejército y la Marina de los E U A, se han estudiado los efectos de la estreptomicina en el tratamiento de unos 4,500 casos de tuberculosis, incluso casi 2,000 de la forma pulmonar. Un planeamiento cuidadoso y una colaboración efectiva han dado por resultado uniformidad en la selección de los casos y en la anotación de resultados.

2 Fueron investigados los efectos clínicos de siete distintos regímenes de estreptomicina, primordialmente con respecto a la toxicidad del antibiótico, el coeficiente de aparición de cepas resistentes del *M. tuberculosis* y el resultado terapéutico. Además, se ha estudiado la dihidroestreptomicina desde diciembre, 1948.

3 Queda demostrado que, rebajando la dosis diaria de estreptomicina de 2.0 Gm. a 1.0 Gm. y a 0.5 Gm., se ha reducido sucesivamente la incidencia de todas las importantes manifestaciones tóxicas, y que disminuyendo la duración de la administración de la droga de 120 a 60 ó 42 días, también se atenúa la toxicidad. Una reducción del número de inyecciones en las cuales se divide la dosis diaria total ha ido igualmente asociada con menor toxicidad. Estas observaciones rezan con la disfunción vestibular, el deterioro de la función renal, la dermatitis, la púrpura medicamentosa y las otras manifestaciones tóxicas discutidas en el texto del trabajo. La dihidroestreptomicina solo fué estudiada en 56 casos, pero parece ser menos tóxica que la estreptomicina con respecto a la función vestibular, aunque en lo demás no discrepar mayor cosa de la sustancia matriz no hidrogenada.

4 Cepas de bacilos tuberculosos resistentes a 10  $\gamma$  por ml. o más de estreptomicina aparecen con bastante regularidad, lo cual parece ser independiente de la dosis diaria dentro de los límites estudiados pero estar claramente relacionado con la duración de la terapéutica. Al cabo de 42 días de administración diaria, aproximadamente 35 por ciento de los ejemplares examinados son resistentes a

γ por ml o más, al cabo de 60 días, 50 por ciento, al cabo de 120 días, 75 por ciento. La administración de estreptomina cada tres días, en vez de cada día, hace bajar a la tercera parte esas cifras de aparición de cepas resistentes. La terapéutica combinada, con el ácido para-aminosalicílico (PAS) agregado a la estreptomina, hace bajar todavía más los coeficientes de aparición de cepas resistentes.

5 Los casos de tuberculosis pulmonar tratados con siete regímenes de estreptomina, esencialmente homogéneos con respecto a pautas tales como período de la enfermedad, tanda de preestreptomina y por ciento de formas cavernosas y de predominio exudativo, manifestaron resultados clínicos de considerable uniformidad, dentro de la variabilidad de los regímenes estudiados.

(a) La fiebre, cuando existía al iniciar el tratamiento, bajó en siete octavos de los enfermos y descendió a lo normal en poco más de la mitad. En tres octavas partes de los casos hubo un aumento de peso de más de 4.5 kg. Las variaciones conforme al régimen seguido no fueron importantes en esos sentidos.

(b) La mejoría radiológica varió de 82 por ciento en los casos tratados con 2.0 Gm diarios por 120 días, a 60 por ciento en los tratados con 0.5 Gm diarios durante 42 días. Entre los tratados durante 120 días, disminuyó poco el porcentaje que muestra los distintos grados de mejoría, a medida que la dosis diaria disminuyó de 2.0 Gm a 1.0 Gm y 0.5 Gm, y a 1.0 Gm cada tres días, bajó más el porcentaje que muestra los grados de mejoría radiológica rotulados como "marcada" y "moderada". Hubo una disminución significativa en el porcentaje de casos clasificados como "marcadamente" y "moderadamente" mejorados en cada categoría posológica diaria (2.0, 1.0 y 0.5 Gm diarios) cuando la duración de la terapéutica fué disminuida de 120 a 60 ó 42 días.

(c) Los coeficientes de recidivas fueron bastante uniformes para los casos tratados con dosis totales mayores y algo más altos para los tratados con 1.0 Gm diario durante 42 días o 0.5 Gm diarios durante 120 ó 42 días.

(d) Las tasas de viraje del esputo en los cultivos fueron notables por lo uniformes con todos los regímenes estudiados, a pesar de la considerable variación en la incidencia de colapsoterapias empleadas en los distintos grupos.

(e) La mortalidad experimentada fué uniforme en los casos tratados con los regímenes más altos en dosis total, levemente mayor en los tratados durante 42 días así como en los tratados con 0.5 Gm diarios durante 120 días.

6 En los casos de tuberculosis extrapulmonar no fué posible estudiar los resultados de las variaciones de la estreptominaoterapia con la misma minuciosidad que en los de tuberculosis pulmonar, debido a ser más pequeño el número de casos y menos completos los datos. Sin embargo, hasta donde fué posible observar, rigieron las mismas tendencias con respecto a las variaciones de régimen que hubo en la tuberculosis pulmonar.

7 Preséntanse los datos relativos al tratamiento de la granuloma y la tuberculosis meníngea, comprendiendo varias alteraciones más de la terapéutica. En tanto que sobreviven unos 30 por ciento de los casos de granuloma 18 meses o más después de iniciar la terapéutica, sólo sobreviven ese tiempo 10 por ciento o menos de los que tienen meningitis tuberculosa (ya haya o no granuloma).

8. En esta memoria se ha hecho hincapié en particular en el efecto de las variaciones del régimen de estreptomycin, reconociendo lo complejo que es el problema de la valuación de los resultados, incluso los estadísticos y los clínicos. La investigación probablemente ha planteado tantos problemas como los que ha resuelto, siendo manifiesto que la justipreciación de la estreptomycinoterapia en la tuberculosis exige el delicado balanceo de muchos factores separados, y en particular los de toxicidad, farmacorresistencia, y las varias facetas de la respuesta clínica.

9. Dedúcese que no se ha determinado todavía que haya un régimen estreptomycinico "mejor". Un gramo diario parece constituir una dosis diaria satisfactoria, pero la duración de la terapéutica, el espaciamiento entre las administraciones y la combinación con otros agentes quimioterápicos dotados de propiedades tuberculoestáticas, son puntos que no han sido aun determinados positivamente. Por virtud de las limitaciones impuestas a la estreptomycinoterapia por el fenómeno de farmacorresistencia, parece que la duración del tratamiento no debe generalmente exceder de 42 ó 62 días, hasta que se hayan normalizado en forma adecuada los procedimientos encaminados a retardar la aparición de cepas estreptomycinorresistentes de bacilos tuberculosos.

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# DIFFUSE PULMONARY GRANULOMATOSIS IN YOUNG WOMEN FOLLOWING EXPOSURE TO BERYLLIUM COMPOUNDS IN THE MANUFACTURE OF RADIO TUBES

Report of Five Cases

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## INTRODUCTION

Five young women, with a history of employment in the manufacture of radio tubes, developed a chronic lung ailment characterized by shortness of breath, cough, high pulse rate, and weight loss. Increasing difficulty in breathing appeared to be the main disabling feature. The illness came on insidiously and the patients became aware of it when they no longer were employed in the radio tube factories.

In the first case no definite ante-mortem diagnosis was made and the nature of the disease became apparent through the autopsy findings. The patient died in May 1944, at a time when a group of workers in a fluorescent lamp factory, Salem, Massachusetts, developed an occupational lung illness. The autopsy material obtained in this case by Dr. Harrison S. Martland was forwarded by him to the late Dr. L. U. Gardner, Saranac Lake, for correlation with the findings in the Salem cases. Beryllium and other components of phosphors were revealed in a specimen of her lungs. Later on, the Kettering Laboratory reported 3.0  $\gamma$  of beryllium in 100 Gm. of wet lung tissue. Part of the pathological report by Dr. Gardner and also the chemical and spectrographic analyses are included in the presentation of this case.

Three patients are alive. One of them had been working for over eight years in three different radio tube plants, in each of which she had been exposed to dust inhalation.

The other 2 patients had been employed for several years in the same plant, where the second patient spent her last fourteen months of factory employment. They had been working in the spray room, where the cathodes, grid hooks, and filaments of the tubes are being coated with a mixture of phosphors.

The fifth case is included in retrospect. She was seen in 1935 and no significance was attached then to her history of employment in a radio tube plant. The diagnosis could not be determined clinically and no autopsy was obtained.

## CASE REPORTS

*Case 1* The patient, C. D., was a 25-year-old, married, white woman. She was first seen on October 29, 1942, when she consulted the writer because of severe shortness of breath.

Difficulty in breathing and a mild cough had begun about one year previously. She became irritable and unduly fatigued at work. She consulted her family physician in December 1941 and on January 3, 1942 her illness was diagnosed as rheumatic heart disease and

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she was advised to give up working and to limit her activities at home. However, medication and rest from work brought no relief. Early in October 1942, while out for a walk, she felt a sudden sharp pain in the chest and became very short of breath. Her temperature had apparently remained normal since the beginning of the sickness. No sputum examinations or chest roentgenograms had been obtained.

The past history was noncontributory, except for an illness in 1938 from May until July when her knees and ankles became swollen and red blotches appeared on her legs. The illness was considered to be rheumatic in nature. The family history was negative for tuberculosis and for rheumatic fever.

The patient began to work in factories at the age of seventeen. In 1934 and 1935 she worked for fourteen months on radio tubes in two different factories. In January 1937 she obtained employment in a plant for the manufacture of telephone equipment. The patient was engaged mainly in removing insulation from copper wires by means of revolving steel wire brushes. Some of the copper wires were made of an alloy containing beryllium. She was not protected against inhaling the dust scattered by the brushes. During 1938 and 1939 she was unemployed and in 1940 resumed the work of removing insulation from copper wires and continued until January 1942, when she became disabled.

The patient was a small, undernourished woman. Her breathing was rapid and shallow. The visible mucous membranes were cyanotic. The fingers were slightly clubbed. The superficial regional lymph nodes were not enlarged. The heart sounds were clear with accentuation of the second pulmonic sound. The liver and spleen were not enlarged.

A chest roentgenogram (figure 1, October 29, 1942) showed that the right lung was collapsed by a pneumothorax occupying the outer one-third of the field. The visible portion of the lung was diffusely infiltrated with nodules. The apex of the upper lobe contained a rarefied area, connected by slender adhesions with the dome of the chest wall. A massive density, apparently representing enlarged tracheobronchial lymph nodes, was present in the root region. The right hemidiaphragm was depressed to a level lower than the left leaf. The costophrenic sinus was clear. The left lung was also diffusely infiltrated with nodules and only its outer basal portion was hyperaerated and did not clearly show the infiltration. The heart was displaced to the left and presented a marked bulge in the region of the pulmonary conus. The bulge was evidently formed by merging shadows of an enlarged right ventricle and of enlarged tracheobronchial lymph nodes.

Four weeks later, following bed rest at home, her chest roentgenogram (figure 2, November 27, 1942) showed the right lung fully re-expanded, with no definite cavity visualized in its upper lobe. Both lung fields were packed with nodular densities, irregular in shape and varying in size from 1 mm. to 1 cm. These large nodules were superimposed on a background stippled with discrete miliary nodules. Minute calcific deposits were visualized in occasional nodules. The apical and costophrenic regions of both lungs contained areas of increased translucency. The horizontal interlobar septum was elevated to the second anterior intercostal space. The right hemidiaphragm rose to a level higher than the left and appeared to be tented. The heart returned to a normal position. The bulge in the region of the pulmonary conus remained unchanged.

Repeated sputum examinations were negative for tubercle bacilli and for fungi. Skin tuberculin tests were also negative.

In the latter part of February 1943, the patient suddenly began gasping for breath and became extremely cyanotic. Physical examination revealed recurrence of the right-sided spontaneous pneumothorax. Oxygen had to be administered intermittently for three to four hours daily.

A chest roentgenogram of April 3, 1943 still showed a residual pneumothorax along the upper outer margin of the right lung. On April 25, 1943 the patient entered a hospital for observation. No definite diagnosis was made. The right lung was again re-expanded and there was no evidence of a pleural effusion. Oxygen inhalation was discontinued during the last two days of hospitalization.

She returned home on May 6, 1943 and two days later the right lung ruptured spontaneously for the third time. Oxygen inhalation was administered constantly day and night (4 to 5 tankfuls weekly) from this time until her death twelve months later.

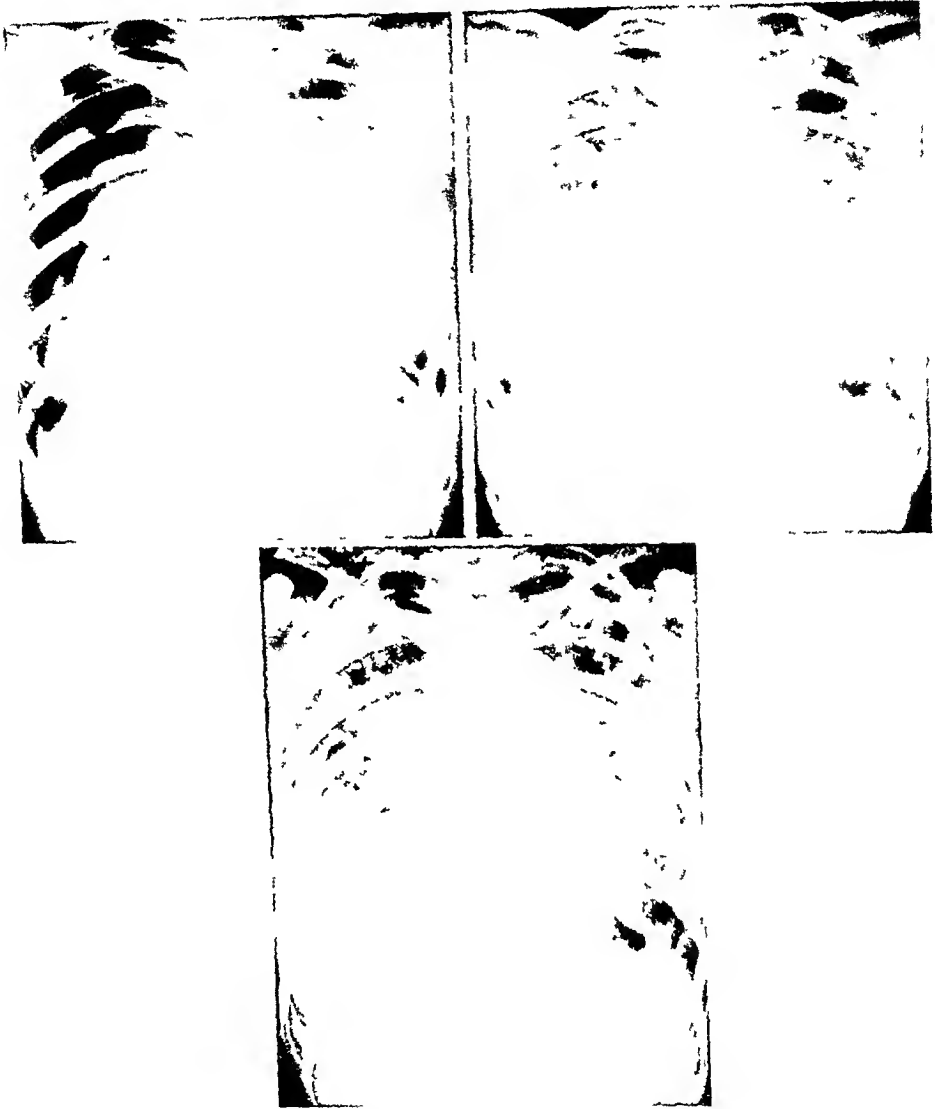


FIG 1 Case 1 (Upper left) October 29, 1942 Right sided spontaneous pneumothorax. Diffuse nodular infiltration. Enlarged tracheobronchial lymph nodes. Cor pulmonale.

FIG 2 Case 1 (Upper right) November 27, 1942 Right lung re-expanded.

FIG 3 Case 1 (Bottom) February 17, 1944 Pattern of nodular infiltration unchanged. Pleural effusion simulating elevated right diaphragm.

A chest roentgenogram of September 13, 1943 showed a pleural effusion at the base of the right lung.

The last chest roentgenogram (figure 3 February 17, 1944) revealed a convex configuration of the basal pleural effusion which simulated an elevated right diaphragm. Areas of

increased translucency were present in the apices of both lungs and in the left costophrenic sinus. The nodular infiltration remained unchanged.

Röntgenographic examination of the bones of both hands was negative.

The temperature continued virtually normal during the entire course of the illness. There was no evidence of the presence of an acute inflammatory process. Her weight came down to 72 pounds, a loss of 38 pounds as compared with her highest weight. The menstrual periods were absent for several months. She remained mentally alert and although continuously under an oxygen mask, managed to do reading and hand sewing.

On May 8, 1944 early in the morning, she asked to be propped up stating that she was no longer able to breathe. She died a few minutes later.

#### POST MORTEM EXAMINATION BY DR. HARRISON S. MARTLAND, MAY 8, 1944

The fingernails were distinctly clubbed. There were no palpable lymph nodes or skin lesions. One pint of straw-colored fluid was found in the abdominal cavity and pelvis. The liver was displaced and extended three finger breadths below costal margin. The diaphragm was opposite the sixth rib on the right side and the fifth rib on the left side.

One pint of straw-colored fluid and a few old adhesions were present in the right pleural cavity. There were a few old adhesions over the apex of the left lung. The pericardial cavity contained 50 cc. of clear yellow fluid. There was marked hypertrophy of the right ventricle, the muscle in the conus being 9 mm. thick. There was no hypertrophy of the muscle of the left ventricle which was only 6 to 7 mm. in thickness. No rheumatic lesions were present on any of the valves. Near the cardiac end of the stomach there was one large node 3 cm. in diameter, which revealed on section the same appearance as the hilar nodes. The liver was small with distinct nutmeg markings. No gastrointestinal lesions were found.

#### REPORT BY DR. HEROLD CARDNER, DECEMBER 1, 1944

*Gross Appearance of Fixed Tissues Submitted.* The pleural surfaces of the right lung were roughened, due to the presence of tags of fibrous adhesions between which were occasional thin-walled blebs projecting above the surface.

The specimen included portions of the upper and middle lobes only. The major part of the former and that part of the middle adjacent to the interlobar fissure were consolidated and contained relatively few patent air spaces. Inspection with a lens revealed numerous discrete grey nodules which were rarely larger than 1 mm. in diameter. These in every way resembled small silicotic lesions. Between them the walls of air spaces were generally thickened, so that the alveoli were greatly reduced in size. Some of this interstitial fibrosis was also nodular in character, but such lesions lacked the definition of the previously described "silicotic" type foci, being much smaller, yellow in color and without dust pigmentation.

Extending downward from the apex was a multilocular cavity with trabeculation due to undestroyed vessels and other band-like structures. On the trabeculae were many minute, yellowish nodules. This cavity which extended within 3 mm. of the pleura had no definite walls and showed no evidence of erosion. The surrounding tissue was either air-containing or in places consisted of conglomerations of grey pigmented nodules.

The middle lobe presented widespread coarse emphysema with intercommunicating blebs as large as 1 cm. in diameter. This change was largely central in the slab of tissue submitted. The margins of the lobe contained more air, but even here a lens revealed thickened alveolar walls with many small colorless and scattered larger discrete grey nodules.

Vessels and bronchi were not remarkable. The bronchial nodes were enlarged moderately firm, grey mottled with yellow. The normal architecture was largely obscured. The surrounding connective tissue was not disturbed.

Examination of the left lung showed a picture similar to that of the right, with the exception of the cavity. There were more and larger discrete nodules of the "silicotic" type in the apex of the upper lobe and many more of the minute, ill-defined yellow nodules



The bronchi and bronchioles appeared quite normal except for distortion by surrounding lesions and in excess of mucus in goblet cells and in some places in the lumen. The epithelium of the smaller air spaces had become cuboidal, where backed by proliferative lesions.

The blood vessel changes consisted of an obliteration of the capillary bed with the persistence of large thin walled arterioles in the newly formed tissue and a moderate to marked degree of endarteritis in many but not all vessels of larger calibre. None were found in which complete obliteration of the lumen had occurred.

The *tracheobronchial nodes* were unusually large and most of their normal architecture had been replaced by lesions similar to those in the lungs. Conglomerate hyaline fibroses had completely replaced the central portion of most nodes, leaving only a thin rim of lymphoid tissue at the periphery. The latter was seeded with small granulomas, either cellular or in various stages of hyaline degeneration. Visible dust was small in amount, but inclusion bodies occurred in the peripheral zone and occasionally within the large central hyaline mass.

*Chemical analysis* revealed the following values:

Zn	Be	Mn	SiO <sub>2</sub>	Mg	W
—	—	—	—	—	—
0.20 per cent	*N 1	**I 1	1.36 per cent	2.78 per cent	Zero
*N I—None found					
**I T—I unit Trace					

*Spectrographic analysis* revealed the following values:

Zn	Be	Mn	SiO <sub>2</sub>	Mg	W
—	—	—	—	—	—
25	5	10	50	60	Zero

**Case 2.** The patient, S. K., was a 35 year old, married, white woman who was first seen by the writer on September 19, 1946.

Her present illness began seven years previously, in August 1939, nineteen months after she had stopped working on radio tubes. Since that time she had been complaining of shortness of breath, productive cough, and weight loss. Repeated examinations in a tuberculosis clinic did not determine the nature of her illness. Sputum tests were negative for tubercle bacilli and for fungi. Skin tuberculin tests were also negative. An operation on her sinuses in 1943 and a tonsillectomy in 1945 brought no relief. A roentgenographic diagnosis of sarcoidosis was made in February 1944.

The history of past diseases was noncontributory. She gave birth to two children. The first was born in September 1938, eight months after she quit factory work. The second child was born in November 1945, six years after the beginning of her present illness. Both deliveries were under spinal anesthesia.

The patient's father died of pulmonary tuberculosis at the age of 52.

The patient began to work in factories at the age of thirteen. At sixteen she worked for eight months on radio tubes. At nineteen she resumed this work and continued for seven and one half years in two different plants, from 1930 until January 1938. Her work included mounting radio tubes, welding parts of the tubes, welding carbon plates to tubes, mounting grids, and finally handling metal plates for fourteen months. Her employment in places other than radio tube factories involved no occupational exposure.

She was undernourished, having lost 34 pounds from a high of 160 pounds. Her breathing was rapid and the visible mucous membranes were slightly cyanotic. The fingers were not clubbed. There was no evidence of skin lesions and the superficial region of lymph nodes were not enlarged. The heart sounds were clear. Adventitious sounds were present over the upper lobes of both lungs and at the base of the right lung. The liver and spleen were not

pulpa ble. The blood pressure was 104 mm. of mercury systolic and 82 mm. diastolic. The vital capacity was 1000 cc.

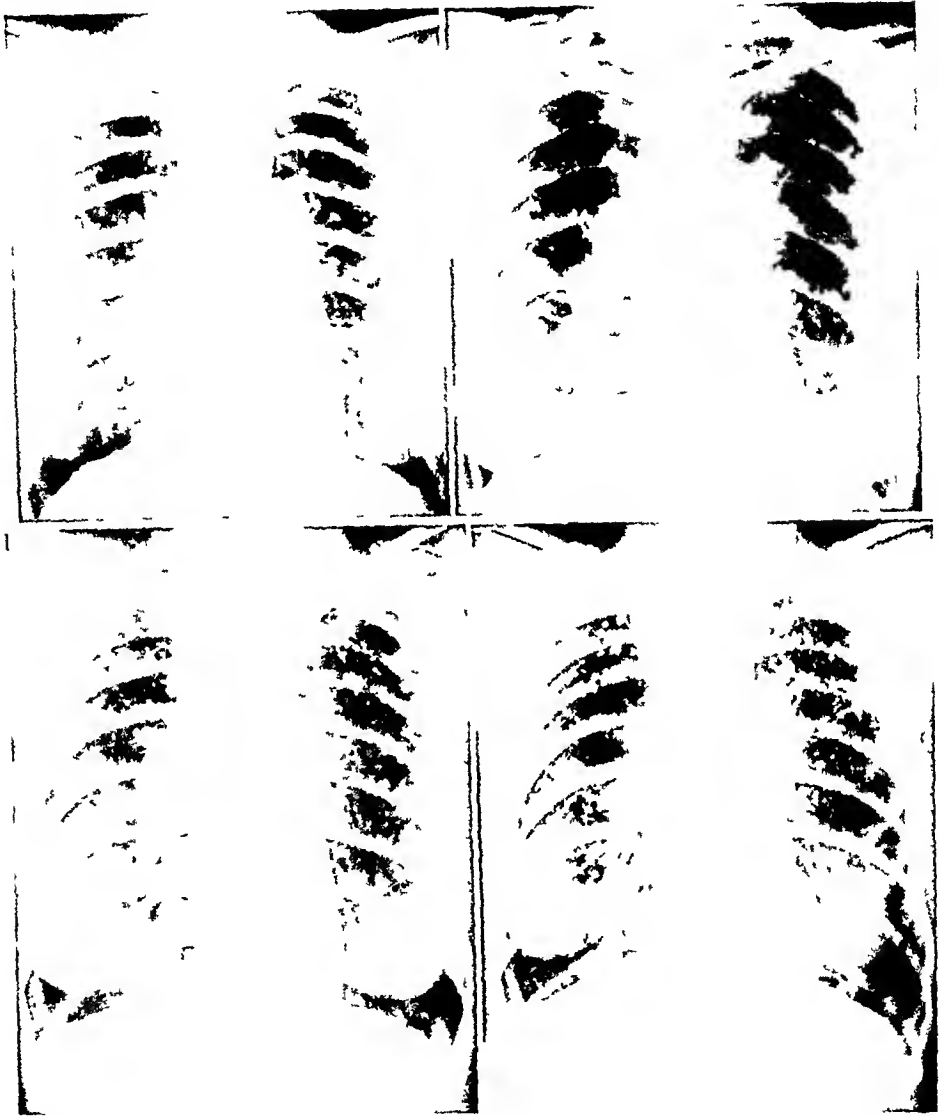


FIG. 4 Case 2 (Upper left) November 8, 1939. Diffuse granular infiltration. Hilum shadows increased in size and density. Heart normal.

FIG. 5 Case 2 (Upper right) January 25, 1941. Diffuse reticulonodular infiltration, overshadowing the original granular nodulation.

FIG. 6 Case 2 (Lower left) February 2, 1949. Disseminated calcification of nodules. Reticulonodular pattern unchanged.

FIG. 7 Case 2 (Lower right) June 19, 1949. Increased calcification of nodules. Tuberculin and histoplasmin skin tests negative. Heart normal.

Her first chest roentgenogram (figure 4, November 8, 1939) showed a diffuse granular infiltration through both lungs. Occasional larger nodules were present among the minute



granules and alongside the vascular markings. The hilar shadows were enlarged and of increased density. The heart shadow was of a normal configuration.

Subsequent chest roentgenograms showed a steadily developing reticulonodular pattern of infiltration, overshadowing the granular nodulation.

A chest roentgenogram, taken four years later (figure 5, January 25, 1944) showed a diffuse reticulonodular infiltration through both lungs. The network was composed of nodular densities and fibrous tissue strands. The background was diffusely stippled with discrete punctate nodules. Calcific deposits were present within some of the larger nodular densities. The tracheobronchial lymph nodes showed no further enlargement. The heart shadow was unchanged.

The chest roentgenograms of October 18, 1941, September 19, 1946, and February 2, 1948, revealed spreading calcification of the nodules.

In January 1949 she missed a menstrual period and in February her urine pregnancy test was positive. She complained of further weight loss and of increasing weakness. Her cough and expectoration were aggravated by the cold weather. The shortness of breath remained unchanged.

The chest roentgenogram (figure 6, February 2, 1949) showed widespread calcification through both lungs, the calcific deposits being embedded within the larger nodular densities. The reticulonodular pattern of infiltration remained unchanged. Miliary granules were still visualized in the background, but most of them were obscured by connective tissue infiltrates and by enlarged areas representing coarse emphysema and blebs. The right costophrenic sinus was blunted. The heart shadow appeared to be narrower.

There was no evidence of continuing invasiveness. The granulomatous reaction was apparently in its final stage of evolution, the stage of stabilized calcifying lesions.

A therapeutic abortion was advised and performed. Foci of necrosis were present in the placenta.

The last examination on June 19, 1949, revealed some improvement in her general condition. With the passing of the cold weather, her cough and expectoration had decreased and she had gained four pounds in weight. The pulse rate was 86 per minute. The heart sounds were normal. Only occasional adventitious sounds were heard over the lungs. The vital capacity was 1,675 cc., as compared with 1,000 cc. during the winter months. The test repeated twice weakened her and ten minutes later her blood pressure was 80 mm. of mercury systolic and 72 mm. diastolic. In another ten minutes readings of 92 mm. systolic and 72 mm. diastolic were obtained.

The chest roentgenogram (figure 7, June 19, 1949) showed additional calcific deposits within the larger nodules. More miliary granulomas became obscured by connective tissue proliferation. The heart shadow appeared to be normal. The hilar shadows were of increased density.

The histoplasmin skin test (1:100 dilution) was negative.

**Case 3.** The patient N. Y., was a 29-year-old, married, white woman who was first seen on June 19, 1948.

In 1945, while still working on radio tubes, she developed shortness of breath on dancing and on climbing. She also began to lose weight. She attributed these changes to married life. In January 1947, six months after she stopped working in the radio tube factory, she developed a productive cough. She was treated for an upper respiratory infection but failed to improve. Her condition grew worse after she became pregnant about one month later. The roentgenographic findings in May 1947 were interpreted as a recent pulmonary infection of unknown origin and she was hospitalized as a pneumonia case. On November 8, 1947, the patient gave birth to her first child. The shortness of breath and cough grew steadily worse. Repeated roentgenographic examinations continued to reveal an obscure pulmonary infection, which showed clearing immediately after childbirth but became aggravated later on. Tubercle bacilli could not be demonstrated in her sputum. The skin

tuberculin tests were reported negative. On June 15, 1948 her illness was diagnosed as possible beryllium granulomatosis.

The history of past diseases was noncontributory.

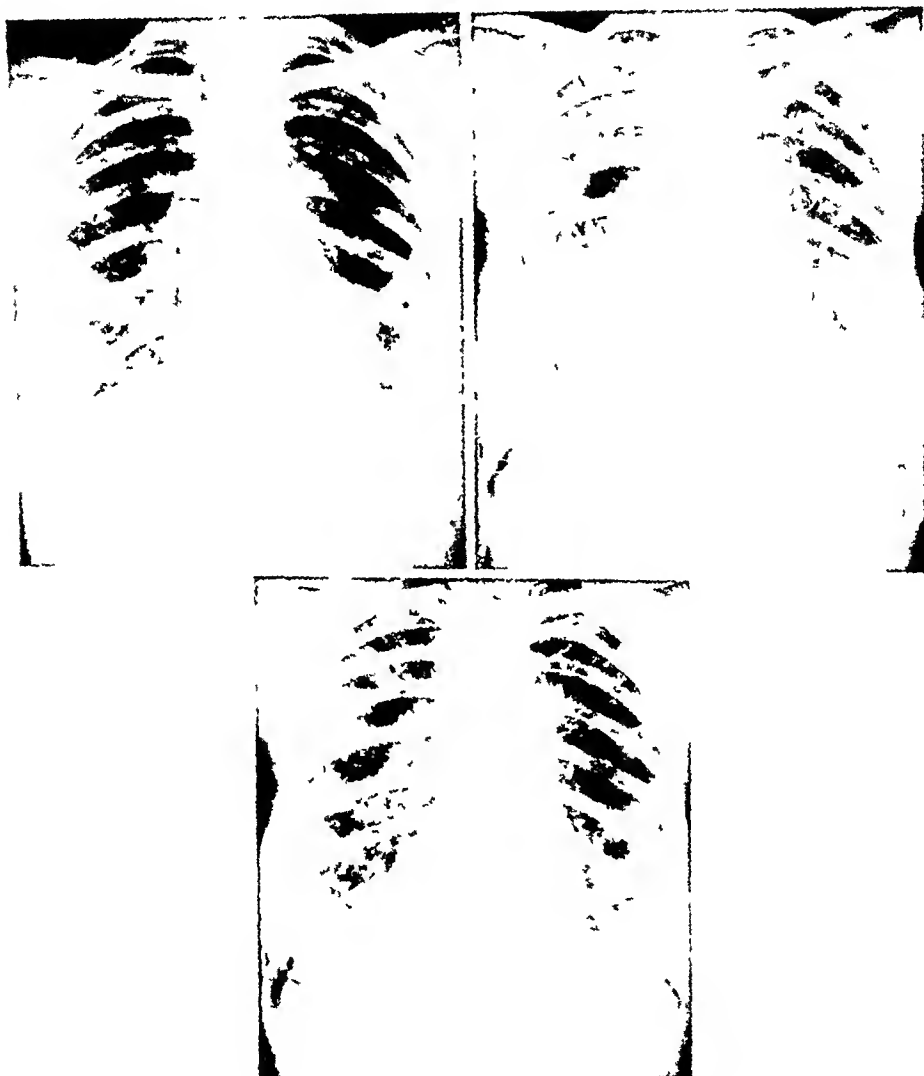


FIG. 8 Case 3 (Upper left) July 14, 1947 Diffuse reticulonodular infiltration. Left border of heart straightened.

FIG. 9 Case 3 (Upper right) November 16, 1948 Increased reticulonodular infiltration. Right diaphragm elevated. Bulge in pulmonary conus.

FIG. 10 Case 3 (Bottom) June 18, 1949 Reticulonodular pattern unchanged. Cor pulmonale.

The family history was negative for pulmonary tuberculosis.

The patient began to work at the age of fourteen. At twenty she worked for eight months on radio tubes. From August 1938 until June 1946, she had been employed continuously in the same radio tube factory where the second patient (Case 2) spent her last fourteen

months of employment. Then, for the first year the present patient was engaged in soldering cups on radio tubes and the remaining seven years she spent in the spray room spraying grid leads for two years and cathodes for the next five years. Her employment in places other than the radio tube factories involved no occupational exposure.

The physical examination revealed shortness of breath and cyanosis of the visible mucous membranes. The superficial regional lymph nodes were not enlarged and there were no skin lesions. The fingers were not clubbed. The pulse rate was 86 per minute. The heart sounds were clear, the second pulmonary sound was accentuated. Adventitious sounds were present over the right lung anteriorly and over the left lower axillary region. The liver and spleen were not palpable. The blood pressure was 112 mm. of mercury systolic and 78 mm. diastolic. The vital capacity was 1,000 cc., or 50 per cent of the normal. The weight was normal 10 pounds less than her highest weight.

Her previous chest roentgenogram (figure 8, July 11, 1947) showed a generalized reticulo-nodular infiltration through both lung fields. The nodules together with fibrous tissue strands formed a dense network, the background of which was stippled by a diffuse miliary nodulation. The hilar shadows were of increased density. The left border of the heart shadow was straightened.

The skin tuberculin test was positive.

Examination on November 16, 1948 revealed a lowering of her vital capacity to 1,200 cc. The chest roentgenogram (figure 9, November 16, 1948) showed increased nodulation in both lungs. The reticulonodular pattern of infiltration remained unchanged. On the right, linear areas of atelectasis were present in the lower lateral portion of the lung and the diaphragm was elevated, causing the nodules to become more crowded than on the left side. The hilar shadows were increased in size and the bronchovascular markings extending into the bases were thickened. There was now a bulge in the region of the pulmonary conus.

The granulomatous reaction was obviously still in the invasive stage.

The last examination on June 18, 1949 revealed some improvement in her general condition. Her cough and expectoration subsided with the coming of warm weather. She had gained three pounds in weight. Her pulse rate was 100 per minute. Only occasional adventitious sounds were heard over either lung. The second pulmonary sound was markedly accentuated. The blood pressure was 101 mm. systolic and 72 mm. diastolic. The vital capacity was 1,500 cc., as compared with 1,200 cc. in November 1948. The test provoked coughing and could not be repeated.

The chest roentgenogram (figure 10, June 18, 1949) showed no increase in the nodulation and no change in the reticulonodular pattern of infiltration. On the right, the linear areas of atelectasis were still present in the lower portion of the lung and the diaphragm remained elevated. The bulge in the region of the pulmonary conus became more prominent.

There was no evidence of continuing invasiveness, but the outlook was unfavorable because of increasing right ventricular enlargement.

*Case 4.* The patient (1-D) was a 26-year-old unmarried white woman who was first seen on June 21, 1948.

In February 1948, fifteen months after she had stopped working in a radio tube factory, the patient noticed some shortness of breath on climbing and became aware of weight loss. In April 1948 she developed a cough and began to raise "lumpy sputum." On June 7, 1948 she consulted her family physician who advised a chest roentgenogram and interpreted the findings as indicative of berillium granulomatosis.

The history of her past illnesses was noncontributory. Repeated skin tuberculin tests were negative.

The family history was negative for pulmonary tuberculosis.

At the age of eighteen the patient had worked for one year as a salesgirl and office receptionist. At nineteen, on March 17, 1941, she began work in the same factory where the third patient (Case 3) was working at the time. The present patient was placed in the spray room and worked there steadily for five years and eight months. For the first two years she

worked on filaments and for the next two years as a utility girl, her work including the spraying of cathodes whenever the regular sprayer was absent. During the last twenty months she worked on loading cathodes. She left the factory on October 15, 1946 to resume office work.

The physical examination revealed shortness of breath. The superficial regional lymph nodes were not enlarged and there were no skin lesions. The fingers were slightly clubbed. The heart sounds were normal. Adventitious sounds were present over the axillary and basal portions of the right lung and over scattered areas of the left lung. The blood pressure was 116 mm. of mercury systolic and 86 mm. diastolic. The vital capacity was 1,900 cc. The weight was 121½ pounds, four pounds below normal and twenty pounds less than in October 1946.

The chest roentgenogram (figure 11, June 21, 1948) revealed a diffuse milary nodulation throughout both lungs with a superimposed, thinly spread network of larger nodules and



FIG 11 Case 4 (Left) June 21, 1948 Diffuse milary nodulation. Beginning reticulo-nodular infiltration. Heart normal.

FIG 12 Case 4 (Right) June 18, 1949 Diffuse reticulonodular infiltration, obscuring the original milary nodulation. Heart normal.

fibrous tissue strands. The root shadows were of increased density. The heart shadow was of a normal configuration. There was a considerable scoliosis with the convexity toward the right.

The granulomatous reaction was still in the early phases of the invasive stage.

Examination on June 18, 1949 revealed progression of the disease. She was still doing office work but complained of increased shortness of breath on slight exertion and after meals. An irritative cough, mucopurulent expectoration, and a sharp pain in the lower portion of the left chest persisted throughout the winter months. She had lost four more pounds in weight. The pulse rate was 72 per minute. The blood pressure was 106 mm. systolic and 88 mm. diastolic. Adventitious sounds were present over major portions of each lung. The heart sounds were normal. The vital capacity was 1,550 cc., a drop of 350 cc. since the examination one year previously.

The chest roentgenogram (figure 12, June 18, 1949) showed considerable connective tissue proliferation through both lung fields, the reticulonodular infiltration overshadowing and

partly obscuring the pulmonary nodulation. The outline of the left diaphragm became irregular. The heart shadow was normal. The hilar shadows were unchanged.

Thus far, there was no evidence of right ventricular enlargement.

*Case 5.* The patient, F. D., was a 21-year-old married white woman who was first seen on May 1, 1936, when she complained of shortness of breath, cough, profuse expectoration, and weight loss.

The roentgenogram (figure 13, May 1, 1936) revealed a peculiar diffuse haziness over shadowing both lung fields and consisting of fine granules. The hilar shadows were not enlarged and were of a normal density. The heart shadow was of a normal configuration.

Another roentgenogram taken two weeks later showed the pulmonary haziness to be increased in density. The sputum was negative for tubercle bacilli.

The patient entered a tuberculosis sanatorium for observation. The hospital records indicate that in 1932, at the age of eighteen, she worked for three months on radio tubes. There was no history of other occupational exposures. Her present illness began in December 1935, three years following the employment in a radio tube factory.

The roentgenogram on admission to the sanatorium (figure 14, June 23, 1936) revealed confluent densities over the lower three-fourths of both lung fields. In some areas scattered larger nodules could be distinguished through the densities. The upper portions of the lungs retained the same haziness which prevailed on the previous films, but the larger vascular markings were surrounded by confluent densities in place of the particulate infiltration. A narrow pneumothorax space separated the upper third of the left lung from the mediastinum and from the dome of the chest. The hilar shadows were obscured. A bulge was present in the region of the pulmonary conus.

She left the sanatorium in September 1936. While there she had repeated febrile attacks, her temperature reaching at one time 102.6° F. Coincident with the febrile attacks were the appearance of confluent densities in the lower portions of the lung fields and around the larger vascular markings. These densities were not stationary and were obviously produced by pulmonary edema. Similar roentgenographic findings were described in the Salem cases (3, 6). Her pulse rate ranged between 108 and 131 per minute. Her weight on discharge was 80 pounds, a loss of 12 pounds since admission. Repeated sputum tests were negative for tubercle bacilli and for fungi. Skin tuberculin tests were also negative.

The roentgenogram on discharge from the sanatorium showed a diffuse granular infiltration in the upper half of each lung field. Some larger nodules were present alongside the vascular markings. Confluent densities, intensified by the heart shadows, were still over shadowing the lower portions of both lungs. The left-sided spontaneous pneumothorax had resorbed. The bulge in the region of the pulmonary conus grew larger. The hilar shadows were still obscured.

She returned to the sanatorium for examination on November 9, 1937. The chest roentgenogram (figure 15, November 9, 1937) showed a diffuse granular infiltration and superimposed scattered clusters of larger nodules throughout both lung fields. The hilar shadows were of a homogeneous density. The right ventricle was markedly enlarged.

She died one month later, on December 13, 1937.

#### COMMENT

The symptomatology of chronic beryllium granulomatosis is dominated by shortness of breath and by cough. The disease bears no signs of an infectious process and runs a progressive course, uninterrupted by remissions. Because of an insidious onset, the patients seek medical advice with the disease usually far advanced.

A clinical diagnosis is based on a history of exposure to beryllium compounds

and on typical roentgenographic findings. Only in the occasional case can the diagnosis be corroborated during life by recovery of beryllium from the urine.



FIG. 13 Case 5 (Upper left) May 4, 1936 Diffuse granular haziness overshadowing lung fields Heart normal

FIG. 14 Case 5 (Upper right) June 23, 1936 Confluent densities over lower three-fourths of lung fields Left sided spontaneous pneumothorax Cor pulmonale

FIG. 15 Case 5 (Bottom) November 9, 1937 Diffuse, predominantly granular infiltration Marked cor pulmonale

The post-mortem findings invariably include demonstration of beryllium in the lung tissue.

*Evidence of exposure to beryllium* It is certain that beryllium compounds had been used extensively in the radio tube factories at the time the five pa-

tients were working there. The factory workers were not protected against inhalation of finely pulverized phosphors. In the spray room, where the cathodes, grid hooks, and filaments of the tubes were being coated with a mixture of phosphors, even the sprayers were not provided with masks.

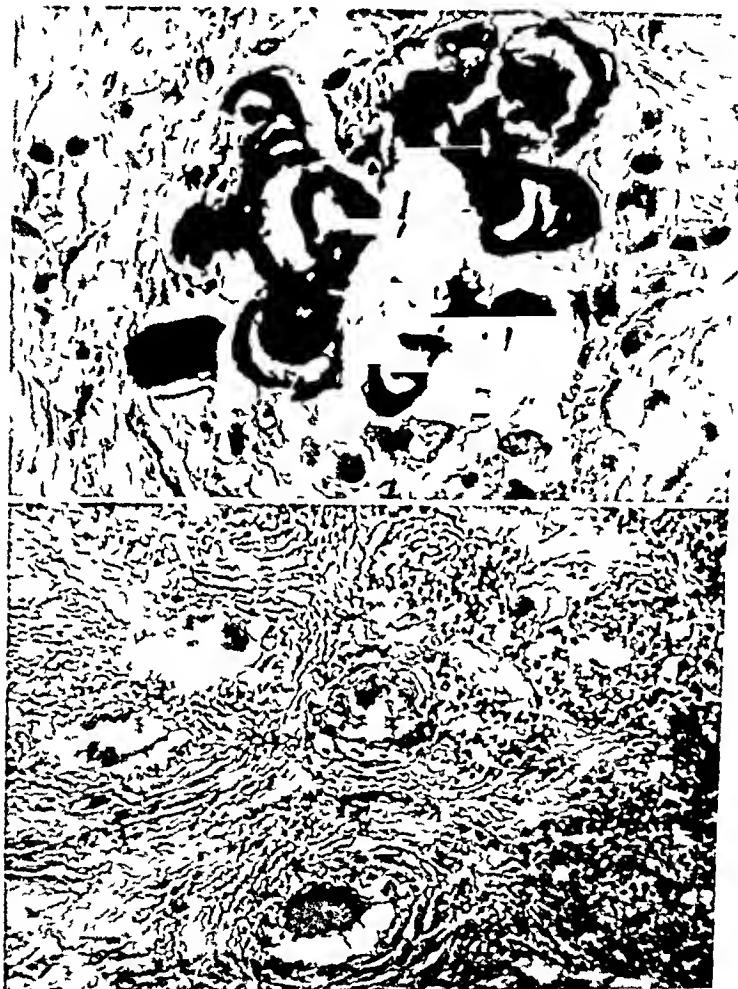


FIG 16 Case 1 (Top) Inclusion bodies lying free in debris of beryllium granuloma

FIG 17 Case 1 (Bottom) Edge of beryllium nodule surrounded by granulation tissue, containing giant cells and acellular tissue infiltrated with lymphocytes

In the first case, the exposure in radio tube factories was incriminated by the presence of beryllium and other components of the phosphors in her lungs. The added exposure in removing insulation from beryllium copper wires was apparently responsible for the finding of inclusion bodies (figure 16) "of the character and frequency, noted only in two cases of beryllium copper casters, lungs" (2).

The structural features of the granulomas (figure 17) served to distinguish

them from silicosis and from silico-tuberculosis (1, 2) The results of the chemical analysis were also negative for silicosis (low ash value of 4.36 per cent) The inclusion bodies differed from those seen in sarcoidosis (2)

The second patient had been exposed to dust inhalation in three different radio tube factories for a period of more than eight years She worked for fourteen months in the same factory, where the next two patients developed a similar illness The nature of the dust could not be specified by the patient, but there was no free silica dust

The third and fourth patients had been working during a concurrent length of time in the spray room of a radio tube factory Both had been directly exposed to an atmosphere laden with pulverized phosphors containing beryllium The exposure of the third patient began one and one-half years earlier and had been more intense because of her work as a full-time sprayer Consequently, her illness became apparent two and one-half years earlier than that of the fourth patient and has resulted in marked heart damage

The relationship of exposure to beryllium and the pulmonary granulomatous reaction is obvious in these two cases and has been further substantiated by the occurrence of additional instances of a similar disease among the workers of the same factory

In the fifth case the details of exposure to dust inhalation in a radio tube factory remain unknown

*Roentgenographic findings* The roentgenographic pattern of the granulomatous reaction was made up of milky and discrete larger nodules, of composite nodular densities, and connective tissue infiltrates Diffuse milky nodulation was present in all cases and probably represented an early phase of invasion This phase in the three surviving patients had been gradually replaced by a reticulonodular pattern of infiltration, composed of larger nodular densities and connective tissue infiltrates In the two fatal cases, connective tissue proliferation was scarce and no distinct fibronodular network was observed

In the first case, large nodules, discrete and conglomerate (figures 18 and 19), were mingled with a diffuse milky nodulation Intervening connective tissue was scarce The pattern of infiltration remained unchanged for a known period of sixteen months

In the second case, roentgenograms were available for a period of nine years and eight months The original milky nodulation has been gradually replaced by a reticulonodular pattern of infiltration

The third case came under observation with a reticulonodular type of infiltration superimposed on a diffuse milky nodulation Within a period of two years the fibronodular network became more diffuse, obscuring most of the minute nodules

The fourth case was first seen with a diffuse milky nodulation and a minimal reticulonodular infiltration Within one year the fibronodular network became more diffuse and overshadowed a large portion of the minute granules

In the fifth case, a diffuse granular infiltration, described as typical in chronic beryllium granulomatosis (3, 5, 6), prevailed in all roentgenograms for a known



period of eighteen months. There was a constant paucity of fibrous tissue proliferation and of composite nodule formations.

None of the cases developed plaques, or massive conglomerations, as seen in silicosis with the advent of severe symptoms.

Deposition of calcium in the granulomas represents apparently the end phase in their evolution. The presence of calcium deposits in some of the nodules was

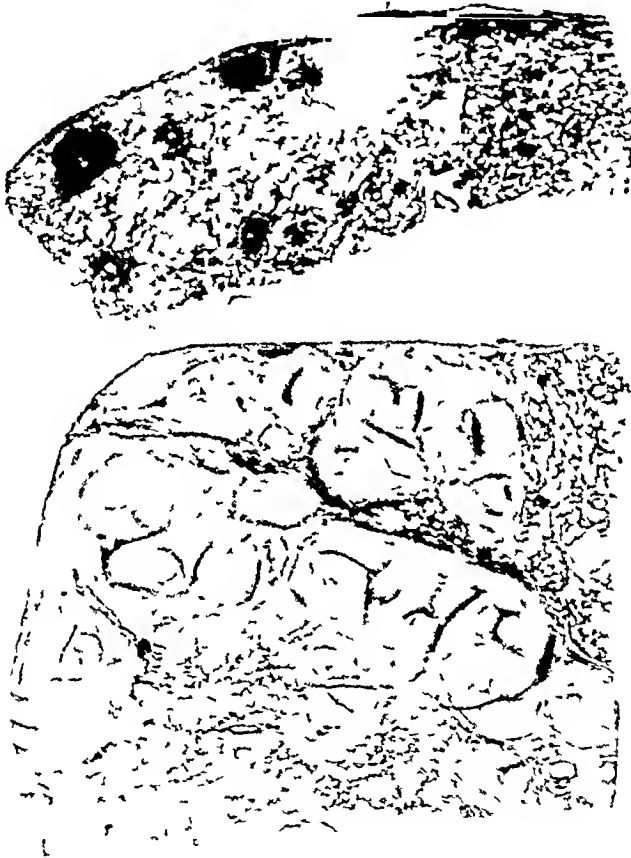


FIG. 18. Case 1 (Top) Discrete beryllium granulomas, 2 to 3 mm. in diameter. Emphysema.

FIG. 19. Case 1 (Bottom) Conglomerate beryllium granulomas, 4 to 8 mm. in diameter. Emphysema.

confirmed by Von Kossa stain in the first case. Widespread calcification of the nodules was obvious in the second case.

Multiple bleb formation was observed in all cases and appeared graphically as rarefied areas surrounded by groups of nodules. A cavity in the upper lobe of the right lung was present in the first case. As stated in the pathological report, "the cavity was either the result of anemic necrosis, or of bleb formation. There is little to indicate that this cavity resulted from necrosis of tissue incident to bacterial infection" (2).

In the third case, the lower portion of the right lung contained linear areas of atelectasis, with a resulting elevation of the diaphragm and crowding of the nodules on that side.

The hilar shadows were increased in size and density, particularly in the two fatal cases. Bronchial lymph nodes in the first case included units measuring 2 cm. in diameter.

*Complications* Spontaneous pneumothorax occurred in both fatal cases. None was observed in the three surviving patients with marked fibrous tissue proliferation. It is possible that the symptoms of a ruptured lung are overlooked in some instances because of pre-existing shortness of breath.

Enlargement of the right ventricle (cor pulmonale) was present in the first, third, and fifth cases. The right-sided pleural effusion in the first case resulted from congestive heart failure. Peritoneal and pericardial effusions were also present.

Continuous mucopurulent expectoration was indicative of bronchiectasis, resulting from distortion of the bronchial tree by the granulomatous process.

*Treatment* The dyspnea and cough were aggravated in all cases by cold weather. Thus, it is believed that a change to a mild climate during the winter months would be beneficial to patients with this illness. Profuse mucopurulent expectoration may be relieved in some instances by antibiotic therapy. Early administration of oxygen relieves dyspnea and cough. As this procedure brings relative comfort to the patient, it may prolong life and prevent the occurrence of spontaneous pneumothorax.

#### SUMMARY

Five cases of chronic pulmonary beryllium granulomatosis are presented, with autopsy findings in one case. The exposure to beryllium compounds occurred in radio tube factories. In the first case, added exposure took place in removing insulation from beryllium copper wires.

The illness appeared to be of lesser severity in cases in which the nodular dissemination was followed by marked connective tissue proliferation.

Calcification of the nodules has been demonstrated in the first and second cases.

#### SUMARIO

##### *Granulomatosis Pulmonar Difusa en las Jovenes consecutivamente a la Exposicion a los Compuestos del Berilio en la Fabricacion de las Ampollas para Radioreceptores*

Presentanse 5 casos de granulomatosis pulmonar cronica por berilio, con los hallazgos autopsicos en uno. La exposicion a los compuestos de berilio tuvo lugar en las fabricas de ampollas para aparatos de radio. En el primer caso, ocurrio nueva exposicion al quitarse el aislamiento de los alambres de cobre-berilio.

La dolencia parecia ser menos grave en los casos en los que la diseminacion nodular fue seguida de marcada proliferacion del tejido conjuntivo.

En el primero y el segundo casos observose calcificacion de los nodulos.

*Acknowledgment*

Acknowledgment is made to Dr. Harrison S. Martland for his generous assistance in the studies of the first case. He performed the autopsy himself and was the first to consider the possibility of beryllium poisoning. The case was briefly reported in his paper (1). Four photomicrographs prepared by him are reproduced in this paper.

Histoplasmin concentrate for skin testing was supplied by Eli Lilly and Company.

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# TUBERCULOSIS AMONG SELECTIVE SERVICE REGISTRANTS<sup>1</sup>

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From the Selective Service records of 18,000,000 men examined for military service during World War II has emerged a wealth of data on physical and mental defects and disease conditions surpassing in scope any other such survey ever made in this country. A by-product of the plan for manpower selection for military service, the picture evolved from this survey has far-reaching significance. Of the defects identified, several were active disease conditions. Among these, one of the most important was tuberculosis. Although this disease is no longer the scourge it was a generation ago, it still is sufficiently prevalent for its frequency among all defects and disqualifying defects of examined men to be of great interest.

## TOTAL REJECTIONS

Tenth among the leading causes for rejection of physically examined Selective Service registrants still under 38 years of age on August 1, 1945, tuberculosis was responsible for 171,300 or 3.5 per cent of all the registrants who were in Class IV-F and classes with "F" designation on August 1, 1945 who constituted the pool of rejected men.<sup>2</sup> This figure represents only rejections for which tuberculosis was the primary cause. It does not include the thousands who had tuberculosis but were rejected principally for some other disqualifying defect, such as syphilis or illiteracy. The percentage of rejections for tuberculosis among white men (3.9 per cent of total white rejections) was more than twice that for Negroes (1.9 per cent) (table 1).

This race difference in the number of men rejected for tuberculosis is explained to some extent by the fact that only one defect was coded as the principal cause of rejection, and that certain disqualifying defects more common among Negroes than among whites were given precedence in designating the principal cause of rejection. Syphilis, illiteracy, and mental deficiency, more common among Negroes than whites, may be used as examples. When associated with tuberculosis, these defects took precedence as principal defects. As a result, the Negro rejection rates for tuberculosis are not strictly comparable to those for whites. The

<sup>1</sup> Based on Selective Service classification data and sample studies of the results of examination recorded on DSS Forms 200, Reports of Physical Examination, for Selective Service registrants physically examined at local boards in peacetime, and DSS Forms 221, Reports of Physical Examination and Induction, for registrants examined at local boards and induction stations in wartime.

<sup>2</sup> Data in this report include only registrants processed for induction or volunteering for induction through Selective Service local boards. They do not include military, naval, or air force registrants who enlisted directly at armed forces' recruiting stations prior to cessation of such enlistments in December 1942, since no physical examination reports for these registrants were received by the Selective Service System.

exact effect of such a factor on the rejection rates is not known, but data on all recorded defects, reviewed in more detail later in this paper, reveal that Negroes had a lower frequency of tuberculosis per 1,000 examined than was true of whites, although the race difference in all recorded defects was less than in rejection rates

#### PROCEDURES OF EXAMINATION AND VARIATIONS IN STANDARDS AFFECTING TUBERCULOSIS REJECTION RATES

Rates of rejection of Selective Service registrants were affected by several important factors. During the total period of procurement there were differences in the average age of the men examined and the proportion of men undergoing re-examination as well as in examination procedures and physical standards.

Standards of acceptability in effect during and immediately preceding World War II were specified by the Army in Mobilization Regulations 1-9.<sup>3</sup> Local board examining physicians as well as Army examiners used these standards in

TABLE 1

*Estimated Number and Per cent of Selective Service Registrants Examined at Ages 18 to 37 and Rejected Because of Tuberculosis and Still under 38 Years of Age on August 1, 1945\**

RACE	TOTAL IN REJECTED CLASSES	REJECTED FOR TUBERCULOSIS†	
		Number	Percent
All races	4,828,000	171,300	3.5
White‡	3,909,000	154,000	3.9
Negro	919,000	17,300	1.9

\* Includes men in Class IV-F and also those in the occupationally deferred classes, II-A(F), II-B(F), II-C(F). Does not include those with disqualifying tuberculosis for whom other defects were recorded as the principal defects.

† Includes registrants rejected because of obviously disqualifying tuberculosis.

‡ Includes all races other than Negro.

the examination of registrants. During peacetime (November 1940 to the end of 1941) two complete physical examinations were given to many registrants, the first of which was given at the local board and the other at the induction station to registrants forwarded for induction. However, chest roentgenograms were not included at the local board examination unless the physician referred the case to a Medical Advisory Board chest specialist for decision. Beginning in the summer of 1941, chest roentgenograms were made routinely at induction stations. Registrants were designated as acceptable, if examination revealed arrested pulmonary tuberculosis consisting of lesions demonstrated by roentgenographic examination as not exceeding the minimal extent defined in the classification of the National Tuberculosis Association.

<sup>3</sup> Mobilization Regulations 1-9, "Physical Standards for Examination during Mobilization," August 1940, March 1942, October 1942, and April 1944, and changes thereto in War Department Circulars and Letters. These standards relating to lungs and chest wall are summarized in "Physical Examinations of Selective Service Registrants, Special Monograph No. 15, Selective Service System, Washington, D. C., 1948, Vol. I, pp. 222-228.

Beginning in January 1942 and continuing through 1943, local board examining physicians rejected, by a screening examination, those registrants obviously disqualified for military service. The arbitrary limits defined by the National Tuberculosis Association as minimal lesions were specified in the Selective Service regulations as the number and size of the apparently healed tuberculous lesions which were acceptable for general military service after induction station examination.

From January 1944 until the end of Selective Service, local board physicians no longer saw each registrant who was called for induction. Instead, registrants who received notices to report to armed forces induction stations for preinduction physical examination might request a local board physical examination, if they believed or knew they had defects which were manifestly disqualifying for military service.

TABLE 2

*Per cent of Total Rejections Because of Tuberculosis and Frequency of Tuberculosis per 1,000 Registrants Examined during Selected Time Periods*  
*Continental United States*

TIME PERIOD	PER CENT OF TOTAL REJECTIONS			FREQUENCY PER 1,000 EXAMINED		
	All Races	White*	Negro	All Races	White*	Negro
November 1940–September 1941†	2 3	2 3	1 5	9 7	10 3	5 2
April 1942–December 1943‡	3 2	3 5	2 0	19 1	19 9	14 6
February 1944–December 1944‡	3 4	3 7	1 9	35 4	36 9	25 6

\* Includes all races other than Negro

† Figures shown are for local board examinations only

‡ Local boards and induction stations

In April 1944 regulations were issued removing the arbitrary limits on the size of the tuberculous lesions, and registrants with calcified residuals of primary tuberculosis were accepted for general service, if the size, number, and character of such lesions did not suggest possible reactivation.

#### TUBERCULOSIS REJECTION AND FREQUENCY RATES AT THREE DIFFERENT PERIODS

The effects of these varying conditions and standards are best illustrated by comparing the results of physical examination in relation to tuberculosis rejection and frequency rates during several short periods of Selective Service experience. During the peacetime period, 2.3 per cent of all rejections at local board examination were made because of tuberculosis (table 2). This was also the rate for whites, but the Negro rate was 1.5. During this period tuberculosis was recorded for 9.7 registrants in each 1,000 examined, 10.3 for whites and 5.2 for Negroes. This, however, did not include an unknown number of registrants in whom tuberculosis was found at the time of examination by Army medical examiners.

The proportion of rejections for tuberculosis during the second period (April

1912–December 1943) increased to 3.2 per cent and the frequency of tuberculosis to 19.1 per 1,000 examined, almost twice as high as in peacetime. From February 1944 through December 1944, 3.4 per cent of all rejections were for tuberculosis and the frequency of tuberculosis was 35.4 per 1,000 men examined.

The increasing rates for both racial groups during the two wartime periods emphasize the value of the induction station examination with the use of the chest roentgenogram as an aid to diagnosis, in sharp contrast to the peacetime examination at local boards without use of roentgenograms. Also, during the war periods the figures on tuberculosis, particularly those for Negroes, were not reduced as much as during peacetime by the tendency of examining physicians to select diagnoses of venereal disease or of educational deficiency as principal causes for rejection. Educationally deficient registrants were acceptable on a quota basis from August 1942 through June 1943, after which time educational deficiency alone was not a cause for disqualification. And those with uncomplicated gonorrhea or syphilis had become acceptable on a quota basis (October 1942–November 1943) or in as large numbers as treatment facilities permitted (after November 1943). As a result, during the war period tuberculous registrants for whom one or both of these defects had been recorded would probably have the tuberculous condition noted as principal cause for rejection.

The figures shown in table 2 reflect not only differences in examination procedures, but also changes in the composition of the examined groups. During the first, or peacetime, period the men examined were 21 through 35 years of age, mostly single men, and occupational deferments were of prime importance. During 1942 and 1943, the men examined were 18 through 44 years of age (18 to 19 years old beginning on November 13, 1942, 20 years old beginning on February 16, 1942, 21 to 35 years old all during years 1942 and 1943, 36 to 37 years old beginning on February 16, 1942, 38 to 44 years old, February 16, 1942 to December 1942), and even occupational deferments were limited to those employed in essential industries or agriculture. During 1944 men examined were largely 18 through 25 years of age. Thus it can be seen that the second period, 1942 and 1943, was probably more representative of the total male population with respect to tuberculosis than were the other two time periods for which information is available.

#### TUBERCULOSIS DATA FOR 1940–1944

The remainder of the present paper provides analyses of Selective Service data on tuberculosis with regard to race, age, specific diagnosis of tuberculosis, occupation, and state of residence. In all of these items except the last, the data used begin with November 1940 and end with December 1944. This is the longest period of time for which Selective Service data on tuberculosis are available, and this is the first time data for this combined period have been published. Furthermore, in order to avoid the inevitable duplications caused by re-examination of registrants, a sample of records was selected so as to contain first examinations only, for the periods November 1940–September 1941, April 1942–September 1943, and November 1943–December 1944. For these reasons, the

TABLE 3

*Rate of Rejection for Tuberculosis per 100 Registrants Examined, by Race and Age Group  
Continental United States*

RACE	AGE GROUPS			
	All Ages	18 to 25	26 to 29	30 and over
November 1940-December 1944				
All races	1 6	1 2	1 5	2 4
White*	1 7	1 2	1 6	2 6
Negro	1 1	1 0	1 0	1 4
November 1940-December 1943†				
All races	1 3	0 8	1 1	2 1
White*	1 3	0 8	1 2	2 3
Negro	1 0	0 8	0 9	1 3
January 1944-December 1944‡				
All races	2 7	2 4	2 9	3 4
White*	2 9	2 5	3 1	3 6
Negro	1 6	1 5	1 5	2 0

\* Includes all races other than Negro

† 1940-1943 data based on a 10.4 per cent sample of DSS Forms 200 (Reports of Physical Examination) for the period November 1940-September 1941, inclusive, and on a 6.7 per cent sample of DSS Forms 221 (Reports of Physical Examination and Induction) for the period April 1943-December 1943, inclusive, they do not include reports of second and subsequent examinations of registrants, to avoid possible duplication of data. Reports for registrants examined and later deferred for other than physical or mental reasons are excluded from the sample.

‡ 1944 data based on an approximately 10 per cent sample of DSS Forms 221 (Reports of Physical Examination and Induction) for registrants inducted or rejected during January 1944-December 1944, inclusive, they do not include reports of second and subsequent examinations of registrants, to avoid possible duplication of data. Reports not available for registrants who were found acceptable on preinduction examinations but were not returned for induction.

data presented in the next few pages are considered to give the most reliable facts on tuberculosis among Selective Service registrants during the period of time specified.<sup>4</sup>

<sup>4</sup> The data published by the Selective Service System on tuberculosis have appeared incidentally in four medical statistics bulletins and one special monograph. The rejection rates and frequency rates found in each of these bulletins cover only a part of the whole time period beginning in November 1940 and ending in December 1944 and in most instances do not eliminate other than first examinations. The four bulletins, published by National Headquarters, Selective Service System, are "Analysis of Reports of Physical Examination," *Medical Statistics Bulletin No. 1*, 1941, "Causes of Rejection and Incidence of Defects," *Medical Statistics Bulletin No. 2*, 1943, "Physical Examinations of Selective Service Registrants During Wartime," *Medical Statistics Bulletin No. 3*, 1944, "Physical Examinations of Selective Service Registrants in the Final Months of the War," *Medical Statistics*



## TUBERCULOSIS REJECTIONS BY RACE AND AGE

For the over-all period the rejection rate on first examination for general military service for registrants of all races, aged 18 to 44 years, was 43.9 per cent. The rate of rejection because of tuberculosis was 1.6 per hundred men examined, and increased regularly within each age group (table 3). The Negro rejection rate for tuberculosis was lower than that for white registrants, a differential maintained in each age category.

Table 3 also reveals race and age differentials for the two periods 1940-1943 and 1944 and the same general race difference for each age group and increasing rates with increasing age. The rates for 1944 were higher in all categories than was true of the 1940-1943 rates. The main reasons for this phenomenon were the more thorough physical examination of men after the speed of mobilization slowed down in 1944 prior to the German counterattack in December 1944, and the fact that educational deficiency and uncomplicated syphilis were no longer the principal cause of rejections, thus causing tuberculosis to be recorded as the principal disqualifying defect in a larger part of the cases examined. Another factor was that the rates after April 1944 did not include records of men aged 26 through 37 years of age who were found acceptable at the time of pre-induction examination, but who were never returned for induction because the armed forces reached their planned strength and lowered the upper age of acceptability of men to 25 years.

## REJECTIONS BY SPECIFIC DIAGNOSES

Study of the specific diagnoses of tuberculosis discloses that 96.4 per cent of a sample of registrants rejected for tuberculosis during the period November 1940-December 1944 had the pulmonary form and only 3.6 per cent had other kinds of tuberculosis (table 4). These proportions were very consistent for each age group and for both whites and Negroes. Moreover, there was no significant difference between race groups in distribution of diagnoses.

About one-third of pulmonary tuberculosis cases were active for the all ages-all races group, and over 43 per cent were arrested, while almost one-fourth were cases unspecified as to whether active or arrested. The proportion of active cases increased with age, as did the unspecified cases, while the percentage of arrested cases, over half of all in the 18 to 25 year group, decreased rapidly as age increased. These same trends were exhibited for both whites and Negroes, except that among Negroes there was no distinct age trend for unspecified diagnoses of tuberculosis.

Two important differences appear in the specific diagnoses for the period 1940-1943, compared with those for 1944. A total of 95.3 per cent of cases were diagnosed as pulmonary in the 1940-1943 period, compared with 98.3 per cent

TABLE 4

*Per cent Distribution of Tuberculosis Rejections, by Specific Diagnoses, by Age and Race Group*  
*Continental United States*

November 1940–December 1944\*

CAUSE FOR REJECTION	AGE GROUPS			
	All Ages	18 to 25	26 to 29	30 and Over
All Races				
Total tuberculosis	100 0	100 0	100 0	100 0
Pulmonary tuberculosis	96 4	96 7	96 0	96 4
Active	31 8	24 4	33 0	38 2
Arrested	43 1	54 0	41 0	33 8
Suspected or unspecified	21 5	18 3	22 0	24 4
Other tuberculosis	3 6	3 3	4 0	3 6
White†				
Total tuberculosis	100 0	100 0	100 0	100 0
Pulmonary tuberculosis	96 4	96 7	96 0	96 3
Active	31 5	24 0	32 8	37 8
Arrested	43 6	54 8	41 7	34 2
Suspected or unspecified	21 3	17 9	21 5	24 3
Other tuberculosis	3 6	3 3	4 0	3 7
Negro				
Total tuberculosis	100 0	100 0	100 0	100 0
Pulmonary tuberculosis	96 7	96 8	95 6	97 0
Active	34 5	27 7	34 5	41 8
Arrested	38 6	47 6	34 9	30 4
Suspected or unspecified	23 6	21 5	26 2	24 8
Other tuberculosis	3 3	3 2	4 4	3 0

\* 1940–1943 data based on a 10.4 per cent sample of DSS Forms 200 (Reports of Physical Examination) for the period November 1940–September 1941, inclusive, and on a 6.7 per cent sample of DSS Forms 221 (Reports of Physical Examination and Induction) for the period April 1942–December 1943, inclusive, they do not include reports of second and subsequent examinations of registrants, to avoid possible duplication of data. Reports for registrants examined and later deferred for other than physical or mental reasons are excluded from the sample. 1944 data based on an approximate 10 per cent sample of DSS Forms 221 (Reports of Physical Examination and Induction) for registrants inducted or rejected during January 1944–December 1944, inclusive, they do not include reports of second and subsequent examinations of registrants, to avoid possible duplication of data. Reports not available for registrants who were found acceptable on preinduction examinations but were not returned for induction.

† Includes all races other than Negro.

in 1944.<sup>5</sup> The same high consistency in the proportion of pulmonary diagnoses in each age group occurred during both periods of time and for each race.

The most outstanding difference between the two periods of time was in the decline in the proportion of unspecified pulmonary cases in 1944, compared with the 1940-1943 period. From one-third of all cases in the 1940-1943 period with unspecified pulmonary diagnoses, the proportion fell to 3.4 per cent in 1944. Almost all of the proportionate increase in specified cases was in the arrested category (from 33.2 per cent of all cases to 58.6 per cent). The decrease in the percentage of unspecified pulmonary tuberculosis in 1944, compared to 1940-1943, was probably a result of the fact that during 1944 virtually all registrants were examined at armed forces induction stations and the examiners were better equipped than were local board examining physicians to determine whether the disease process was active or arrested.

The same upward trends with age for active pulmonary diagnoses and downward trends for arrested cases were found for each of the two periods of examination, but there was no trend with age in either period for the unspecified cases. These facts also apply to each race group in each of the two periods.

#### FREQUENCY OF TUBERCULOSIS

The employment of modern improved methods of diagnosis in the vigorous campaign waged against tuberculosis within the past several decades has disclosed many latent cases. Hence it is impossible to draw a valid comparison between the frequency of tuberculosis during the two world wars. Tuberculosis was recorded for 4.9 out of every 1,000 of the first million men examined in World War I and for 19.8 per 1,000 Selective Service registrants examined, November 1940-December 1944. In view of the fact that the national death rate from tuberculosis has declined sharply in the period between the two wars, the increased frequency of tuberculosis in Selective Service registrants appears to reflect the improvement in methods of detection.

Timely discovery of the disease during World War II examinations not only kept out of service men whose military contributions would have been ineffectual, but also put many tuberculosis cases under remediable treatment leading to potential recovery. The effect of improved diagnosis shows up in disability discharges also. Thus, whereas tuberculosis, as the largest single cause, accounted for 10.9 per cent of all disability discharges during World War I, only about 2.6 per cent of the veterans of World War II, who were receiving disability awards in September 1944, had tuberculosis as their major disability.

Information on the frequency of disease is invaluable in supporting the establishment of any plan for control and eventual elimination of the disease. Keener insight into the problem of tuberculosis is afforded by data on the number of cases found among each 1,000 men examined, regardless of acceptance or rejection for induction. Table 5 presents such data on the frequency of occurrence of

<sup>5</sup> In order to conserve space, tables showing the differences between the 1940-1943 and 1944 data have been omitted. These data are available to interested readers at National Headquarters, Selective Service System.

TABLE 5

*Frequency of Specific Diagnoses of Tuberculosis per 1,000 Registrants Examined, by Race and Age Group*  
*Continental United States*

November 1940–December 1944\*

CAUSE FOR REJECTION	AGE GROUP			
	All Ages	18 to 25	26 to 29	30 and Over
All Races				
Total tuberculosis	20 1	14 7	19 2	30 5
Pulmonary tuberculosis	19 4	14 2	18 4	29 5
Active	6 2	3 4	6 1	11 3
Arrested	8 9	8 0	8 0	10 8
Suspected or unspecified	4 3	2 8	4 3	7 4
Other tuberculosis	0 7	0 5	0 8	1 0
White†				
Total tuberculosis	20 8	15 0	19 8	32 5
Pulmonary tuberculosis	20 1	14 5	19 0	31 4
Active	6 3	3 4	6 2	11 9
Arrested	9 3	8 3	8 4	11 6
Suspected or unspecified	4 5	2 7	4 4	7 9
Other tuberculosis	0 7	0 5	0 8	1 1
Negro				
Total tuberculosis	15 5	12 9	15 2	19 7
Pulmonary tuberculosis	15 0	12 6	14 5	19 2
Active	5 2	3 6	5 2	7 9
Arrested	6 3	6 3	5 9	6 6
Suspected or unspecified	3 5	2 7	3 4	4 7
Other tuberculosis	0 5	0 3	0 7	0 5

\* 1940–1943 data based on a 10.4 per cent sample of DSS Forms 200 (Reports of Physical Examination) for the period November 1940–September 1941, inclusive, and on a 6.7 per cent sample of DSS Forms 221 (Reports of Physical Examination and Induction) for the period April 1942–December 1943, inclusive, they do not include reports of second and subsequent examinations of registrants, to avoid possible duplication of data. Reports for registrants examined and later deferred for other than physical or mental reasons are excluded from the sample. 1944 data based on an approximate 10 per cent sample of DSS Forms 221 (Reports of Physical Examination and Induction) for registrants inducted or rejected during January 1944–December 1944, inclusive, they do not include reports of second and subsequent examinations of registrants, to avoid possible duplication of data. Reports not available for registrants who were found acceptable on preinduction examinations but were not returned for induction.

† Includes all races other than Negro.

tuberculosis at time of first examination by specific diagnoses among men examined at 18 to 44 years of age during November 1940–December 1944.

Table 5 shows that approximately 20 out of every 1,000 men examined were

found to have tuberculosis in some form, 6 of whom had active pulmonary cases, 9 arrested pulmonary cases, and 4 unspecified pulmonary cases, while less than one per 1,000 had tuberculosis of parts of the body other than the lungs. All of these rates rose with age.

Negroes had lower occurrence rates of all sorts than was true for whites, except for active cases among men 18 to 25 years of age, where the difference was small. Another white-Negro difference was that there was no clear relationship between age and the frequency of arrested cases of pulmonary tuberculosis among Negroes, while there was an increase in rates with increasing age among whites. And a third was the failure of Negroes to show a consistent increase with age in the frequency of forms of tuberculosis other than pulmonary.

When the November 1940-December 1943 experience is separated from that of 1944, a few important differences in frequency rates are noticed. The rates for the earlier period were less than half as large as for 1944, but at the same time there was a great reduction in the proportion of cases with unspecified pulmonary tuberculosis.<sup>6</sup> The proportionate increase in arrested pulmonary tuberculosis discovered was particularly pronounced, doubtless because of improved techniques and the universal use of roentgenography in diagnosis during all of the 1944 period.<sup>7</sup> The only other noteworthy difference was that in 1944 there was no consistent increase in the frequency of arrested pulmonary tuberculosis with age for the Negro group, but the white and all race groups showed a regular increase with increasing age in this form of diagnosis.

#### OCCUPATIONAL DIFFERENTIALS IN OCCURRENCE OF TUBERCULOSIS

Analysis of physical examination data by occupation reveals considerable differences in frequency rates. The unemployed and those who did not report occupation had the highest over-all frequency rates (table 6). Also over the average for all groups were professional workers, proprietors, service workers, and craftsmen, while laborers and farmers were below average.

The rates increased in size in most occupational groups with increasing age, the exceptions being domestic service workers and farm laborers and foremen.

There was great variability in frequency rates by occupation for the two major racial groups. Although Negroes had a smaller rate than whites for all occupations, they surpassed whites in rates for clerical and sales workers, and protective service workers.

Analysis by period of time reveals that the high rate of tuberculosis frequency for most of the groups mentioned above was characteristic of both the 1940-1943 and 1944 periods of examination.<sup>8</sup> The age differentials by race and occupation also seem to have been general in both periods of time.

<sup>6</sup> In order to conserve space, tables showing the differences between the 1940-1943 and 1944 data have been omitted. These data are available to interested readers at National Headquarters, Selective Service System.

<sup>7</sup> In this connection should be cited the special effort made by personnel of the Office of the Surgeon General of the Army to diffuse throughout all examining stations comparable use of diagnostic techniques.

<sup>8</sup> In order to conserve space, tables showing the differences between the 1940-1943 and 1944 data have been omitted. These data are available to interested readers at National Headquarters, Selective Service System.

TABLE 6  
*Frequency of Tuberculosis Per 1,000 Registrants Examined in Each Major Occupational Group, by Race and Age Group*  
*Continental United States*  
 November 1940-December 1944\*

OCCUPATIONAL GROUP	RATE PER 1,000 EXAMINED											
	All Races				White†				Negro			
	All Ages	18 to 25	26 to 29	30 and over	All Ages	18 to 25	26 to 29	30 and over	All Ages	18 to 25	26 to 29	30 and over
All occupations	20 1	14 7	19 2	30 6	20 8	15 0	19 8	32 5	15 5	12 9	15 2	19 7
Professional and semiprofessional	21 9	13 8	18 0	33 6	22 4	14 0	18 3	34 7	11 3	7 3	12 2	13 9
Proprietors, managers, and officials	24 2	9 3	16 6	33 1	24 5	9 4	16 8	33 5	9 6	5 3	6 3	11 8
Clerical and sales	19 6	11 7	17 9	33 9	19 5	11 4	17 7	33 9	25 1	19 2	26 9	35 3
Domestic service workers	21 0	16 8	9 6	27 0	36 6	33 1	26 0	39 9	15 6	12 4	5 9	21 2
Protective service workers	25 8	15 1	25 5	30 6	25 6	14 2	25 0	30 8	31 4	37 0	42 6	25 2
Other service workers	24 0	15 7	21 9	33 0	27 3	15 5	23 5	38 9	18 6	16 0	19 3	21 5
Craftsmen, foremen, and kindred workers	21 7	15 5	20 0	29 9	21 8	15 4	19 9	30 5	19 4	16 4	21 7	21 2
Operatives and kindred workers	18 3	13 5	18 5	29 0	18 5	13 3	18 7	30 2	17 0	14 8	16 8	20 0
Farmers and farm managers	16 1	12 8	13 5	21 9	17 3	14 0	14 0	23 1	9 9	6 9	11 2	14 4
Farm laborers and foremen	16 0	15 4	13 4	19 9	17 4	16 7	13 5	22 5	11 3	10 6	13 3	12 1
Laborers other than farm	15 0	12 0	13 0	21 1	16 2	12 4	16 0	24 3	12 5	11 0	9 8	15 8
Students	15 5	15 2	21 4	26 1	15 6	15 3	21 6	25 9	13 6	13 3	17 9	29 4
Noneclassifiable	9 9	6 5	9 6	17 5	10 2	6 5	10 6	18 0	7 5	6 4	—	14 2
Unemployed and emergency workers	32 4	22 6	33 3	51 2	34 9	24 1	36 5	55 6	21 2	15 0	19 6	32 8
Unknown	36 7	30 4	35 0	48 6	38 9	32 7	36 1	51 6	26 8	19 9	29 8	35 7

\* 1940-1943 data based on a 10 4 per cent sample of DSS Forms 200 (Reports of Physical Examination) for the period November 1940-September 1941, inclusive, and on a 6 7 per cent sample of DSS Forms 221 (Reports of Physical Examination and Induction) for the period April 1942-December 1943, inclusive; they do not include reports of second and subsequent examinations of registrants, to avoid possible duplication of data. Reports for registrants examined and later deferred for other than physical or mental reasons are excluded from the sample. 1944 data based on an approximate 10 per cent sample of DSS Forms 221 (Reports of Physical Examination and Induction) for registrants inducted or rejected during January 1944-December 1944, inclusive; they do not include reports of second and subsequent examinations of registrants, to avoid possible duplication of data. Reports not available for registrants who were found acceptable on preinduction examinations but were not returned for induction

† Includes all races other than Negro

TABLE 7

*Frequency of Tuberculosis Defect Per 1,000 Selective Service Registrants Physically Examined by State and Race*

November 1940-December 1943\*

STATE	TOTAL	WHITE†	NEGRO
United States, Continental	15 5	15 9	12 7
Alabama	9 5	7 4	12 5
Arizona	49 3		
Arkansas	18 0	19 1	15 6
California	22 6	22 3	29 0
Colorado	24 5		
Connecticut	10 9	10 7	17 0
Delaware	16 5	17 3	13 5
District of Columbia	18 4	19 6	16 3
Florida	9 8	11 8	7 4
Georgia	7 1	5 1	10 6
Idaho	6 7		
Illinois	21 1	21 0	22 6
Indiana	20 9	20 7	25 6
Iowa	9 5		
Kansas	7 0	6 9	8 4
Kentucky	25 6	25 2	29 5
Louisiana	10 4	11 0	9 6
Maine	9 9		
Maryland	18 4	19 6	14 6
Massachusetts	14 0	13 9	20 8
Michigan	12 7	12 3	19 3
Minnesota	9 8		
Mississippi	6 6	8 3	5 3
Missouri	18 0	17 8	19 7
Montana	9 9		
Nebraska	13 1		
Nevada	13 6		
New Hampshire	9 4		
New Jersey	11 4	11 5	10 4
New Mexico	43 5		
New York City	17 5	17 3	20 1
New York (except N Y C)	15 6	15 6	18 1
North Carolina	7 1	8 2	5 0
North Dakota	9 1		
Ohio	19 7	19 4	24 3
Oklahoma	9 4	9 4	9 6

\* 1940-1943 data based on a 10 4 per cent sample of DSS Forms 200 (Reports of Physical Examination) for the period November 1940-September 1941, inclusive, and on a 6 7 per cent sample of DSS Forms 221 (Reports of Physical Examination and Induction) for the period April 1942-December 1943, inclusive, they do not include reports of second and subsequent examinations of registrants, to avoid possible duplication of data. Reports for registrants examined and later deferred for other than physical or mental reasons are excluded from the sample.

† Includes all races other than Negro. Separate data for whites and Negroes not shown for the states having less than 0 3 per cent of the total U S Negro registrants in the first, second, third, fifth and sixth registrations.

TABLE 7—*Continued*

STATE	TOTAL	WHITE†	NEGRO
Oregon	12 1		
Pennsylvania	13 8	13 8	14 0
Rhode Island	21 2		
South Carolina	5 7	6 7	4 5
South Dakota	10 2		
Tennessee	18 0	18 6	15 9
Texas	15 4	16 6	11 3
Utah	2 9		
Vermont	11 7		
Virginia	17 9	19 9	13 7
Washington	14 8		
West Virginia	26 1	26 0	27 1
Wisconsin	14 2		
Wyoming	4 9		

## VARIATIONS BY STATE OF RESIDENCE

According to the records of men given physical examination during the period November 1940–December 1943, the frequency of tuberculosis was lowest in Utah (only 2.9 per 1,000 men (table 7)). In general, greater freedom from tuberculosis seems to be found in western and northwestern states and in some of the southern states. Wyoming, South Carolina, Mississippi, Idaho, Kansas, Georgia, North Carolina, and North Dakota showed a low rate for tuberculosis. The frequency rate was higher than the national average of 15.5 in Arizona, New Mexico, West Virginia, Kentucky, Rhode Island, Illinois, Indiana, Ohio, District of Columbia, Maryland, Missouri, Arkansas, Virginia, New York City, and Delaware. Migrations of many tuberculous patients to such states as Colorado, California, New Mexico, and Arizona, and many from other states undoubtedly affect the rates to some extent. The amount of such an effect could not be determined, however, without information being available on place of residence at time of the appearance of the disease and date of change of residence to state of registration.

In several states the frequency of tuberculosis per 1,000 registrants examined was higher for Negroes than for whites. Most of such states were in the North and West, where the crowding of low-income Negro groups in city slums may have been a factor in the larger rates. On the other hand, several of the southern states revealed very low tuberculosis rates for Negroes, largely a result of their rural occupation and place of residence. Exceptions to this rule were Alabama and Arkansas where Negro rates for tuberculosis were at or above the national average. The explanation of these and other state variations is not readily apparent from available information, but it is obvious that a number of factors are needed to explain the state and Negro-white differentials.

## SUMMARY

The outstanding facts regarding tuberculosis in the health picture developed from Selective Service records may be summarized as follows:



1 Tuberculosis was tenth in importance as cause for rejection and responsible for 171,300 or 3.5 per cent of all rejections of examined men aged 18 to 37 as of August 1, 1945

2 Rejection data were affected, to some extent, by ages of men examined, changes in physical examination procedures, and changes in physical standards. A potent factor affecting increase, both in rejections and in frequency of tuberculosis discovered during the war years, was the use of the chest roentgenogram.

3 Specific diagnoses of tuberculosis indicate that 96.4 per cent of tuberculosis rejections were for pulmonary tuberculosis during 1940-1944, and that about one-third were for active pulmonary tuberculosis.

4 The marked increase in recorded cases of tuberculosis during World War II, as compared with World War I, is indicative of progress in methods of diagnosis, particularly the use of the chest roentgenogram.

5 Out of every 1,000 men examined through Selective Service during 1940-1944, 20.1 were found to have some form of tuberculosis. Negroes, throughout Selective Service experience, showed lower rates for tuberculosis than did white men.

6 The rejection rate for tuberculosis and the frequency of the disease per 1,000 men examined tended to increase as age increased. This was true for both Negroes and whites.

7 Rejection and frequency rates were higher in 1944 than in 1940-1943 because of statistical factors affecting the computation of the rates.

8 Unemployed men, proprietors, and protective service workers showed the highest frequency of tuberculosis per 1,000, and laborers and students the lowest. Those engaged in out-of-doors work generally manifested less susceptibility to the disease than white collar workers. The rates were generally lower for Negroes than whites in most occupations, and increased with age.

9 State comparisons show that the frequency of tuberculosis was lowest in Utah (2.9 per 1,000 examined) and, except for New Mexico and Arizona, highest in West Virginia and Kentucky, with rates per thousand of 26.1 and 25.6, respectively. Nineteen states had frequency rates above the national average of 15.5 per 1,000 examined during the period November 1940-December 1943.

#### SUMARIO

##### *Tuberculosis entre los Inscritos para el Servicio Militar Selectivo*

Los datos sobresalientes con respecto a tuberculosis que aparecen en el cuadro sanitario formado por los protocolos del Servicio Militar Selectivo, pueden resumirse en esta forma:

1 La tuberculosis ocupa el décimo puesto en importancia como causa de rechazos, habiendo motivado 171,300, o sea 3.5 por ciento, de todos los rechazos de sujetos examinados de 18 a 37 años, hasta el 1° de agosto de 1945.

2 Los datos de rechazo fueron afectados, hasta cierto punto, por la edad de los sujetos examinados, las modificaciones de los procedimientos de examen físico y las modificaciones de las pautas físicas. Un factor potente que afectó el

aumento, tanto en rechazos como en la frecuencia de tuberculosis, fué el empleo de la radiografía torácica

3 Los diagnósticos específicos de tuberculosis indican que 96.4 por ciento de los rechazos por tuberculosis fueron por tuberculosis pulmonar durante 1940-1944, y aproximadamente la tercera parte por tuberculosis pulmonar activa

4 El decidido aumento en los casos de tuberculosis inscritos durante la II Guerra Mundial, comparada con la I, refleja el adelanto realizado en los métodos de diagnóstico, y en particular el empleo de las radiografías torácicas

5 De cada 1,000 individuos examinados por el Servicio Selectivo durante 1940-1944, 20.1 mostraron tener alguna forma de tuberculosis. Los negros, en todas las observaciones del Servicio, revelaron coeficientes de tuberculosis más bajos que los blancos

6 El coeficiente de rechazos por tuberculosis y la frecuencia de la enfermedad por 1,000 sujetos examinados tendió a aumentar a medida que avanzaba la edad, lo cual rezó con negros y blancos

7 Debido a factores estadísticos que afectaron la computación de las tasas, los coeficientes de rechazos y de frecuencia fueron más altos en 1944 que en 1940-1943

8 Los desocupados, los propietarios y los empleados en servicios de resguardo revelaron la mayor incidencia de tuberculosis por 1,000 y los trabajadores y los estudiantes la menor. Los dedicados a trabajos al aire libre manifestaron en general menos susceptibilidad a la enfermedad que los empleados en oficinas, tiendas, etc. Las tasas fueron generalmente más bajas para los negros en la mayoría de los oficios y avanzaron con la edad

9 Comparaciones por estados revelan que la incidencia de tuberculosis alcanzó el mínimo en Utah (2.9 por 1,000 examinados), y aparte de Nuevo México y Arizona, el máximo en la Virginia Occidental y Kentucky, con coeficientes de 26.1 y 25.6, respectivamente, por 1,000. Diecinueve estados mostraron coeficientes superiores al promedio nacional de 15.5 por 1,000 examinados durante el período de noviembre, 1940-diciembre, 1943

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# Case Reports

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## PULMONARY ALVEOLAR ADENOMATOSIS<sup>1 2</sup>

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### INTRODUCTION

In March 1945 David A Wood and Philip H Pierson (1) reported the first case of pulmonary alveolar adenomatosis in which the diagnosis had been made before death. In this patient the diagnosis was established by a lobectomy which was done by Dr Emile Holman six months prior to death. This case was a unique contribution to the literature because the diagnosis was not only made ante mortem but the possible virus etiology of the disease was considered and studies were made in the attempt to prove the etiological factor. Largely because of the interest aroused by this patient and the fact that one of us was able to follow the case with Pierson at the time of his study, it was possible to arrive at diagnosis prior to operation in the case here reported.

Pulmonary alveolar adenomatosis is said to be a rare disease in man, although probably sixteen authenticated cases have now been reported. Among the cases so far reported are those of Lohlein (2), Sims (3), Obendorfer (4), Helly (5), Bonne (6), Richardson (7), Briese (8), Bell (9), Taft and Nickerson (10), three additional cases reported by Paul and Ritchie (11), and three by Drymalska, Thompson, and Sweany (12). Two of the human cases reported were associated with extension to the peribronchial lymph nodes. The etiology of the human disease is still in doubt and the pathogenesis is far from clear. The disease is certainly rare but bears a remarkable resemblance to benign pulmonary adenomatosis which has been reported as occurring epizootically in the sheep of South Africa, Iceland, England, and the United States, especially in certain areas of Montana. Characteristically the disease appears when sheep are being driven from place to place, hence the South African name "Jaagsiekte" or "driving disease." In Montana it has been called progressive pneumonia. The disease was first discovered in South Africa in 1893. It appeared for the first time in Iceland in 1934 and then spread so rapidly that it aroused widespread interest. Apparently it can be introduced into uninfected flocks by sick animals and it is said that animals which merely occupy the quarters previously occupied by infected animals may themselves become ill. In sheep, both sexes and all ages appear to be susceptible. There is only one instance in the literature in which mitoses have been observed in "Jaagsiekte."

For the most part the disease is very insidious and runs a chronic course. Several weeks may pass before it is suspected. Early disease is, therefore, customarily missed, especially if the flock remains at rest. In the later stages the breathing is said to cause a characteristic sound which resembles "slowly boiling porridge" due to the moist rales which may be audible at some distance. Ultimately, secretion pours from the mouth.

<sup>1</sup> From the Departments of Medicine and Surgery, University of California Medical School, San Francisco.

<sup>2</sup> Presented before the Medical Section, as part of the symposium on *Nontuberculous Diseases*, at the 45th annual meeting of the National Tuberculosis Association, Detroit, Michigan, May 5, 1949.

and nostrils and the sheep stand with lowered heads to free themselves of secretion. The incubation period is said by Dingell to vary from six to eight months and Dingell was impressed by a possible hereditary factor. Attempts to demonstrate the etiological agent either virus or bacterial, were uniformly negative. Intrapulmonary inoculation has been said to be a successful method for transfer of the disease in one of three attempts with farm animals. However, housing sheep together appears to lead to transmission without difficulty. The histological factor consists of characteristic epithelial proliferation with formation of papillary intra-alveolar masses which are not invasive but preserve the stromal outlines of the alveoli.

#### CASE REPORT

The patient is a white married female, 51 years of age. Her family history, marital history, and past history until eight or nine years ago seemed to be entirely noncontributory except that in 1939 or 1940 her neighbors had a small flock of sheep which fell ill with an acute type of pulmonary infection from which many of the sheep died. The patient's contact was casual, involving an interest in the misfortune of her neighbors but not to the extent of any care of the sick animals. At about this time, however, or shortly thereafter, she noticed the appearance of a dry hacking cough which was irritative and nonproductive. She believes that in 1941 or 1942 she began to raise small amounts of clear, mucoid, frothy sputum and that at the same time her cough became rather more prominent. She consulted a physician because of her pulmonary symptoms at that time. Her physical examination was essentially negative but roentgenographic examination was said to show some abnormal findings in the region of the right lower lobe, although the film was lost or misplaced and could not be obtained for comparison with subsequent roentgenograms. The diagnosis at this time was bronchiectasis involving the right lower lobe. Meanwhile, however, her symptoms gradually became worse. The sputum increased although it remained mucoid and frothy. In 1944 her symptoms became more severe and a film of this date was also said to reveal a pathologic process in the right lower lobe and bronchograms were said to show bronchiectasis. In 1945 the cough became still more marked and the right lower lobe lesion again appeared in the roentgenogram. This film, dated June 6, 1945, revealed an area of increased density roughly triangular in shape, lying just above the diaphragm and posterior to the interlobar septum between the right middle and lower lobes (figure 1). A bronchoscopy was essentially negative. The sputum, which up to this time had been glairy, white mucus, became thick, yellow and foul smelling and the patient described a troublesome musty odor. She was also troubled by vague right lower chest pain which was never pleuritic in character.

A film taken in July 1946 revealed slight enlargement of the shadow previously described in the film a year earlier. A year later, however, in July 1947, the anteroposterior film (figure 2) revealed a shadow which looked more extensive but nevertheless similar to the preceding ones, although the latter film showed that the process behind the interlobar septum had apparently cleared. The area of density now occupied a triangular area lying against the posterior chest wall, the area above the diaphragm being free. A film taken on December 15, 1947 did not differ from that taken in July of the same year.

Examination of the blood showed the hemoglobin to be 101 per cent, red blood cells 4,970,000 per cu mm, white blood cells 14,150 per cu mm, with a differential count of polymorphonuclears 86 per cent, eosinophils 1 per cent, basophils 0, lymphocytes 9 per cent, and monocytes 4 per cent.

Because of the previous rather casual exposure to sick sheep, the long insidious illness to which no other etiology could be ascribed, and the striking resemblance of the patient to the Wood and Pierson case reported in 1945, a diagnosis of pulmonary alveolar adenomatosis was made. Since no therapy had heretofore proved effective in this disease and since it appeared to be limited to the right lower lobe, right lower lobe lobectomy was agreed upon. Accordingly, on May 4, 1948 the right lower lobe was removed. It was found

to be quite free firm throughout, salmon-pink in color, with a peculiar, smooth, solidified surface. The pathological report follows:

*Material from Right Lower Lobe Lobectomy*

*Gross description* The specimen consisted of a right lower lung lobe, weight 470 Gm., with a smooth pleural surface. The lung parenchyma was very soft and mushy with a salmon-pink color. In many areas it had a pearly-white, granular appearance. Often the alveoli appeared to be distended with this mucoid material. A small portion of the most



FIG 1 (Top) Triangular density right lower lobe posterior to interlobar septum, June 6, 1945

FIG 2 (Bottom) July 17, 1947. Original area lying posterior to interlobar septum has cleared. Density now occupies posterior half of right lower lobe.

superior portion showed true normal congested lung tissue. The bronchi were free from tumor and a few small pigmented hilar lymph nodes were present.

*Microscopic* The alveoli showed varying degrees of metaplasia and replacement by a simple columnar type of mucus secreting cell. The cells were somewhat hypertrophic but well differentiated and mitoses were uncommon. Varying degrees of differentiation were present and occasionally well formed goblet cells were found. The cells frequently had a polypoid appearance. The alveoli were often distended by these cells. The uninvolved alveoli often were distended with mucus and mucoid containing macrophages. Occasional groups of chronic inflammatory cells were noted with early fibrosis of the alveolar walls.

The bronchioles were somewhat dilated and often contained mucus. At the margin of the more normal lung noted grossly, the pulmonary parenchyma was compressed and the nearby alveoli were distended with many large reticulo-endothelial cells with finely granular cytoplasm. There were large numbers of eosinophils and considerable intra-alveolar bleeding. The bronchioles and bronchi in this region also were compressed and the smaller blood vessels showed perivascular cuffing with chronic inflammatory cells and eosinophils. The pleura showed an increased number of chronic inflammatory cells. The hilar lymph nodes showed only moderate anthracosis with a slight increase in the number of eosinophils.

The diagnosis was pulmonary adenomatosis.

Following lobectomy the patient made an uneventful recovery. She apparently remained well until February 1949, when a slight discomfort appeared in the right posterior chest and she noticed a recurrence of the glairy mucoid sputum which had previously characterized her disease. A chest film revealed several areas of density in the lower part of the remaining lung. In March 1949 she returned for examination and sputum samples were taken by Dr. Henry Bruneid of the University of California staff for virus studies which are now being carried out. Following the collection of these sputum specimens the patient was given a ten-day course of aureomycin in one-half gram doses every six hours without apparent clinical effect. Fine crepitant rales were present over the lower right chest following the completion of the aureomycin therapy and the shadows on the roentgenogram showed no definite change.<sup>3</sup>

#### DISCUSSION

While this disease is rare, the writers are of the opinion that it may be somewhat more common than heretofore believed, and it is, therefore, thought worth while to report this patient as one in whom the diagnosis was seriously considered prior to operation. If the disease is of true virus etiology, it is interesting to speculate upon the possible effect of some of the new antibiotics. It is quite possible that opportunities may arise for their trial in the future since the disease is not always localized to one area of the lung but may appear simultaneously in different lobes.

The case for virus etiology is still presumptive. Certainly there is a definite similarity between the morphological appearance of human cases and bovine disease. There is a strong case for the virus etiology of the latter since the transmission from animal to animal appears to be well recognized. So far, however, there is no known recorded instance in which transmission has occurred from man to man.

Is there any relationship between this disease and so-called primary alveolar cell carcinoma of the lung? So far this question remains unanswered. Certainly there are many points of similarity, as will be noted from the microphotograph (figure 3). Nevertheless, the paucity of the mitotic figures and the absence of stromal invasion in our case are more characteristic of pulmonary alveolar adenomatosis. Apparently the hyperplasia of columnar epithelium is primary and stromal changes secondary. An excellent review of the disease as it occurs in Icelandic sheep may be found in Wood and Pierson's article and is therefore, not repeated here. In the same article appears an excellent discussion of the case for and against virus etiology.

Dymalski, Thompson, and Sweeney state that there are no signs or symptoms pathognomonic of pulmonary adenomatosis. Radiologically they say the condition simulates

<sup>3</sup> Shortly after operation sputum from this patient was submitted to Dr. Henry Bruneid of the University of California for virus studies. It was not possible to isolate a virus from the submitted material. Treatment with two standard courses of aureomycin produced no change in the patient's condition. Treatment with 1 Gm. of streptomycin daily for 60 days produced no objective change. The patient is still under observation.

tuberculosis, carcinoma, or pneumonia. In our own case, however, we believed that there were certain features which pointed to the diagnosis. The insidious onset with the long, rather benign course, which was not characteristic of any other chronic pulmonary infection, was suggestive. The fact that the disease appeared to involve the anterior part of the right lower lobe and then shifted to the posterior part of the right lower lobe appeared to be unlike true neoplasm. Nevertheless, the fact that the shadows on the chest roentgenogram never diminished in size, as in atelectasis, seemed to exclude bronchial obstruction. No etiological agent could be recovered from the sputum.

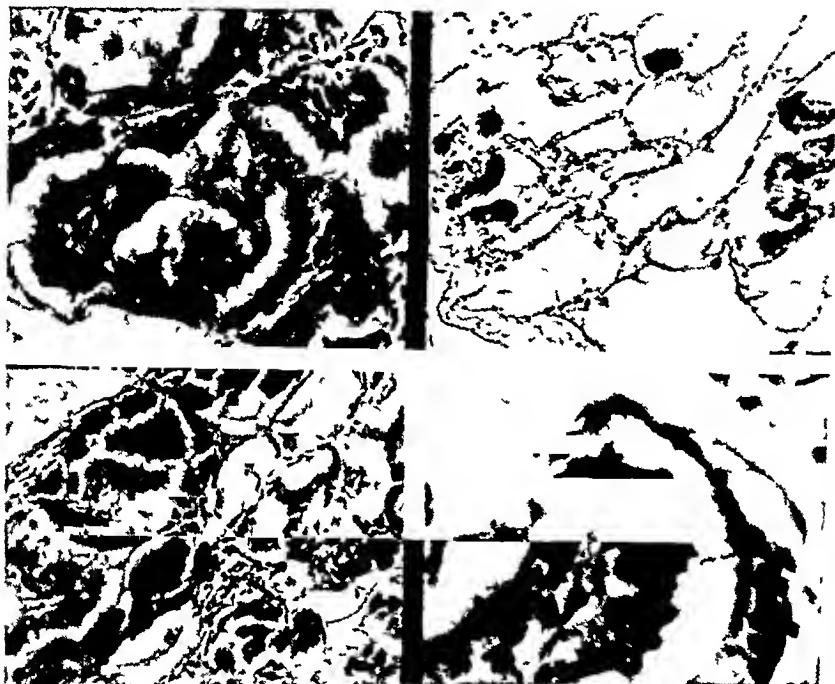


FIG. 3. Alveoli show varying degrees of metaplasia and replacement by a simple type of mucus-secreting cell.

#### SUMMARY

1. A case of histologically benign pulmonary adenomatosis occurring in the right lower lobe of a 51-year-old, white, married female has been reported.
2. This woman had a definite, though rather casual, exposure to sick sheep shortly before her symptoms began.
3. This is the third recorded human case in which the disease has been diagnosed prior to death and the first case to our knowledge in which the correct diagnosis of the disease has been considered prior to operation.
4. In this case the disease appeared to be limited to the right lower lobe at operation.
5. Symptoms appeared approximately seven years before operation.
6. The onset was insidious, characterized by a dry cough gradually becoming productive, with the late development of dull pain over the involved area.
7. The roentgenographic findings were not characteristic of any other disease. The lesion was not one which produced atelectasis but the involved area remained essentially normal in size unlike most other inflammatory processes.

8 Lobectomy has not produced a cure in that there appears to be a spread of the disease into the remaining lung on the operated side seven months following operation.

#### SUMMARY

##### *Adenomatosis Alveolopulmonar*

1 The case communicated is of adenomatosis pulmonum histologically benign in the lobule inferior derecha de una mujer blanca casada, de 51 años.

2 La mujer estuvo manifestamente algo fortuitamente expuesta a ovejas enfermas poco antes de comenzar sus síntomas.

3 Este es el tercer caso comunicado en que se diagnosticó la enfermedad antes de la muerte y el primero en que se consideró el diagnóstico acertado antes de operar.

4 En este caso la infección parece estar limitada al lóbulo inferior derecho al operar.

5 Los síntomas aparecieron aproximadamente siete años antes de la operación.

6 La infección fue insidiosa, caracterizándose por un tos seca que paulatinamente se volvió húmeda y aparición tardía de dolor sordo sobre la zona afectada.

7 Los hallazgos radiográficos no fueron característicos de ninguna otra dolencia. La lesión no fue tal que produjera atelectasia, sino que, en contraposición a otros procesos inflamatorios, la zona comprometida permaneció esencialmente normal en tamaño.

8 La lobectomía no ha obtenido la curación, pues parece haber propagación de la enfermedad al resto del pulmón del lado operado a los siete meses de la intervención.

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# FATAL TENSION PNEUMOTHORAX RESULTING FROM DIAPHRAGMATIC RUPTURE IN A PATIENT RECEIVING PNEUMOPERITONEUM<sup>1</sup>

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In recent years pneumoperitoneum with or without concomitant phrenic nerve interruption has attained considerable favor in the treatment of some types of pulmonary tuberculosis. The occasional complications that may occur such as an embolism, ascites, peritonitis, formation or aggravation of hernia, tear of peritoneal adhesion, mediastinal emphysema, atelectasis, diarrhea, gastric distress, and more can be easily prevented with proper technique, or satisfactorily managed if they occur (1, 2). The purpose of the present paper is to report a fatal case of rupture of the diaphragm in a patient with pneumoperitoneum. To our knowledge, this complication has not been previously reported in the literature although Anderson and Winn refer to the possibility of rupture occurring as a result of an erosive, ulcerative tuberculous process of the diaphragm (3).

## REPORT OF A CASE

D. D., a colored female, 16 years of age, was admitted to the Wm. H. Maybury Sanatorium on December 31, 1946 with a history of productive cough, night sweats and weight loss for six weeks. Physical examination revealed a well developed and well-nourished colored girl appearing chronically ill. Impaired percussion and bronchovesicular breath sounds were found over the upper third of the left lung along with an occasional post-tussive rale. Urine and blood examinations were essentially normal. Sputum tests were positive for tubercle bacilli. Chest roentgenogram on admission revealed a moderately advanced tuberculous process involving the upper two thirds of the left lung with many small areas of rarefaction in this area. A roentgenogram taken four weeks after admission showed further progression of the disease (figure 1). Bronchoscopy on May 6, 1947 was essentially negative. The patient was carried on a conservative regimen of bed rest until May 9, 1947 when pneumoperitoneum was induced with the view of temporizing until the pneumonic character of the disease subsided. The pneumoperitoneum was induced and maintained without difficulty, resulting in an elevation of the left hemidiaphragm a maximum of two and one-half interspaces (from the tenth rib to the seventh interspace posteriorly) and the right hemidiaphragm two interspaces (tenth to eighth interspace). In October 1947 there was an increase in symptoms and a "spread" was seen in the base of the left lung, the right lung remaining clear. The patient received 84 Gm. of streptomycin from October 31, 1947 to January 22, 1948 with considerable symptomatic improvement. Pneumoperitoneum refills of 1,000 to 1,500 ml. of air were continued at weekly or ten day intervals without difficulty, maintaining the diaphragms at the aforementioned levels (figure 2).

In February the possibility of surgical collapse was considered and on February 16, 1948 the refills were temporarily discontinued to allow some depression of the diaphragm so that better roentgenographic visualization of the involved lobes of the left lung could be obtained. On the afternoon of March 11, 1948, twenty days after her last refill, the patient noted rather sudden onset of mild subcostal pain aggravated by deep respiration but unaccompanied by dyspnea. She received sedatives and spent a comfortable night, having only slight pain the next morning. Roentgenographic examination at this time, however, revealed partial collapse of the right lung, with a small amount of fluid at the base. There was displacement of the heart and trachea to the left. The pneumoperitoneum was still present but it was considerably less than at the time of the last refill (figure 3). Careful

<sup>1</sup> From the Wm. H. Maybury Sanatorium, Northville, Michigan.

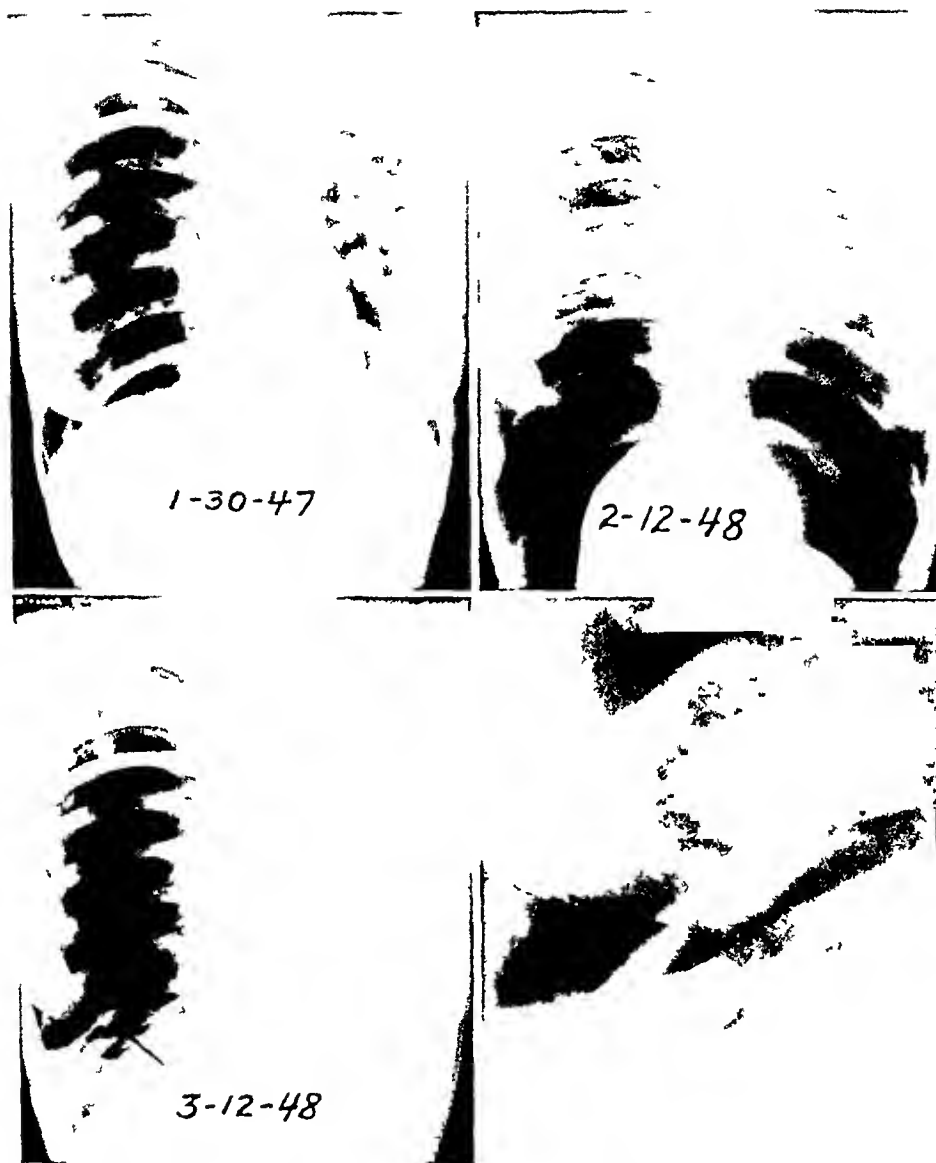


FIG 1 (Upper left) Roentgenogram showing extent of disease before collapse therapy was instituted

FIG 2 (Upper right) Roentgenogram showing elevation of diaphragm following pneumoperitoneum

FIG 3 (Lower left) Roentgenogram showing first spontaneous pneumothorax. Arrow points to bleb like shadows on pleural surface of diaphragm

FIG 4 (Lower right) Enlargement of blebs shown in figure 3

examination of the roentgenogram revealed two adjacent, bleb like shadows, each 7 mm in diameter, projecting above the middle of the right leaf of the diaphragm (figures 3 and 4)

Air was aspirated from the right chest and the lung was allowed to re-expand. The

patient was started on a second course of streptomycin in an attempt to prevent complications. The pneumoperitoneum refills were then cautiously resumed to demonstrate whether or not a diaphragmatic rupture might be present. After small refills on April 5 and April 7, 1948, pressures in the peritoneal space were plus 4 and plus 6. A roentgenogram taken April 8 did not reveal any air in the right pleural space and the bleb-like shadows on the right leaf of the diaphragm were no longer visible (figure 5). During the next six weeks refills were continued and the previous elevation of the diaphragm was gradually attained. Since there was still no evidence of rupture, the pneumoperitoneum was continued as a therapeutic measure with moderate clearing of the pulmonary lesions during the next four months (figure 6).

On September 8, 1948 the patient received her usual refill of 1,300 ml. of air with initial pressures of plus 3, plus 5, and final pressures of plus 6, plus 8. Both diaphragms were well elevated (figure 6). During the day of September 16, it was observed that the patient was exceptionally boisterous laughing, and moving about in bed considerably. At 9:30 that

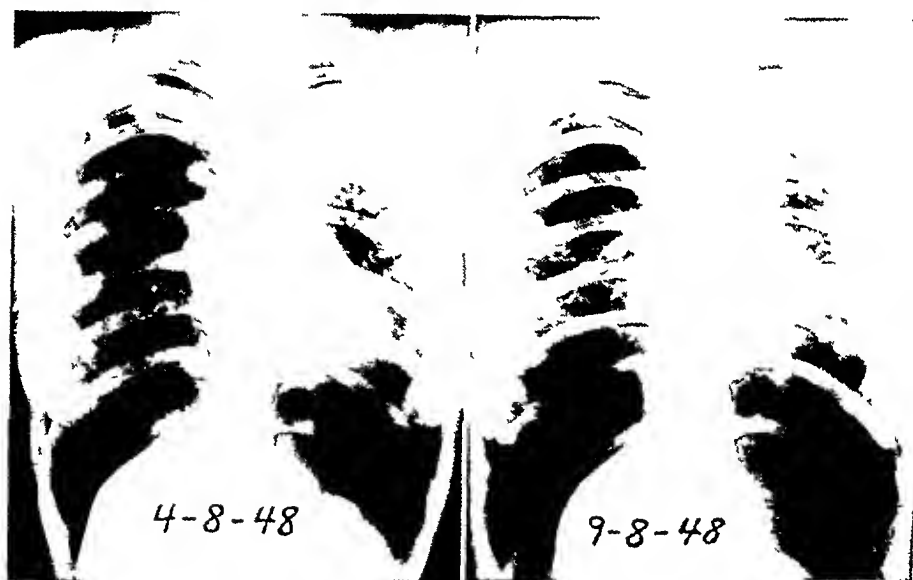


FIG 5 (Left) Roentgenogram showing conditions when pneumoperitoneum was resumed

FIG 6 (Right) Roentgenogram showing elevation of diaphragm immediately after last refill

evening she became somewhat apprehensive and complained of mild right shoulder pain for which she received sedatives. There was no noticeable dyspnea. At midnight her pulse rate was 92, respirations 24, and the patient appeared normal except for nervousness and mild pain. Additional sedatives were given. At 2:30 a.m. the patient raised a small amount of blood-streaked sputum. At 3:10 a.m. her respirations seemed more labored although the rate was 26 and pulse 100. The patient turned on her right side at 3:30 a.m. and was found dead at 3:50 a.m. A post-mortem roentgenogram was obtained (figure 7).

*Post-mortem findings.* Examination of the body revealed a well developed and well nourished colored girl appearing somewhat older than her stated age. Aside from pallor of the lips and mucous membranes, no external abnormalities were found. Before making any incision, a needle connected with a manometer was inserted through the right chest wall and a pressure of 14 cm. of water was registered. A free air space was not found when the needle was inserted through the abdominal wall. Upon opening the abdomen the peritoneal surfaces appeared congested. Numerous small bubbles of air were found trapped behind the omentum. The right diaphragm was convex downward and reached the level of

the sixth rib anteriorly, the liver edge being pushed down 10 cm below the costal margin. The left diaphragm was found at the level of the fourth rib. A second pressure reading of the right hemithorax, taken after the peritoneal cavity was opened, was 8 cm of water.



FIG 7 (Top) Post-mortem roentgenogram. Arrow points to bleb on diaphragm.

FIG 8 (Lower left) Post-mortem photograph. Arrow points to bleb on diaphragm.

FIG 9 (Lower right) Post-mortem photograph showing probe passed through opening on peritoneal aspect of diaphragm.

Incision into the right chest permitted the rapid escape of air. The lower two-thirds of the right lung was found collapsed against the mediastinum which, in turn, was shifted considerably to the left. The upper third of the lung was only partially collapsed, being held in place by dense pleural adhesions present in this area. The right lung was red and

meaty in consistency. It was devoid of crepitation except in the apical region. No tuberculous lesions were found. The left lung showed small emphysematous areas in the apical region and in portions of the lower lobe. Much of the lung was dark red in color, completely devoid of air. On section, numerous old, caseous foci, varying in diameter from 2 to 15 mm, were found in the lower portion of the upper lobe and the adjacent portion of the lower lobe. These lesions were surrounded by atelectatic and partially fibrosed lung tissue.

A soft, whitish mass, 1.7 cm in length and 0.7 cm in diameter, which collapsed under pressure, was found projecting from the pleural surface of the right diaphragm. The mass was located in the middle portion of the diaphragm where the lateral muscle fibers join the central aponeurosis (figures 7 and 8). Pressure against the liver caused clear, yellow fluid to drip from the tip of the projection. On either side of the latter and several centimeters from it, small tags of fibrous tissue were found adhering to the diaphragm. These tags corresponded in position to similar tags found on the diaphragmatic surface of the right lung. On the peritoneal surface of the diaphragm was found a round opening, 2 mm in diameter, which communicated with the bleb-like projection on the pleural surface. This opening lay between two diaphragmatic muscle bundles which appeared widely spread in this area (figure 9). The remainder of the diaphragm was of usual thickness and structure.

The heart showed marked dilatation of the right ventricle. A persistent thrombus weighing 60 Gm. was found. No other abnormalities of importance were found.

A histological section through the bleb on the diaphragm showed a hollow structure about 7 mm in diameter. Its wall, about 1.0 mm thick, was composed of a core of newly formed fibrous tissue with a granulomatous surface on either side. The layer of granulomatous tissue was heavier on the inside (continuous with the peritoneum) and, on this surface, a subacute inflammatory reaction was evident.

The immediate cause of death was given as tension pneumothorax and right-sided myocardial dilatation following rupture of the diaphragm.

#### DISCUSSION

Because of its unusual nature, some explanation of this case seems indicated. The first episode of tension pneumothorax caused considerable discussion as to whether this was the result of a rupture through the diaphragm or a "spontaneous" pneumothorax of the usual variety. The arguments for "spontaneous" pneumothorax were (1) the relatively high frequency of this type of accident in patients with pulmonary tuberculosis as compared with the previously unheard-of occurrence of diaphragmatic rupture, and (2) the continued presence of pneumoperitoneum immediately after the episode and its persistence even after the lung was completely re-expanded. The arguments favoring rupture of the diaphragm were (1) the somewhat rapid decrease in size of the pneumoperitoneal air space, (2) the bleb-like shadows on the superior surface of the right hemidiaphragm, and (3) the lack of demonstrable tuberculosis in the patient's right lung which might conceivably have caused the usual type of "spontaneous" pneumothorax. After this first accident, thoracoscopy was considered to determine if a rent in the diaphragm actually existed but was dismissed in favor of further small pneumoperitoneum refills under careful observation. When no air was demonstrated in the right pleural space after these refills (figure 5), it was concluded that a diaphragmatic rupture was not present. In retrospect it seems evident that the opening in the bleb was closed by the organization of fibrin in the 25-day interval between the first accident and the time when the refills were resumed.

This case history presents other aspects which appear perplexing. Rupture through the diaphragm might be expected to occur during or immediately after a pneumoperitoneum refill when the intraperitoneal pressure is at a maximum, but in the present case the rupture did not occur until twenty and nine days, respectively, after the preceding

refill. It will be remembered that the patient's diaphragm was maintained at a fairly high level for ten months before her first episode of rupture. During this period the muscle fibers were apparently stretched apart sufficiently to permit a small rupture through the diaphragm, resulting in the formation of a bleb on its pleural surfaces. The work of Anderson (4) on the intrapleural pressure changes during pneumoperitoneum may indicate why this bleb ruptured so long after the previous refills were given. He demonstrated that intrapleural pressures were elevated immediately after a refill of pneumoperitoneal air and gradually readjusted to a normal pressure by the time the next refill was given. Therefore, although the highest intraperitoneal pressure is obtained immediately following a refill, the differential pressure between the intrapleural and intraperitoneal spaces may be greatest sometime later.

Two other factors should be mentioned as possibly precipitating the rupture of the bleb at such long intervals after the previous refills. As the diaphragm descended, the relationship of the bleb to the base of the right lung changed. This may have been sufficient to break a seal that had been established between these two structures. Secondly, it appears from the case history that the coughing, laughing, and boisterousness of the patient the evening before she died was an important factor in initiating the terminal episode of rupture. It is probable that the bleb was ruptured by the pull or tear of already stretched adhesions during this excessive activity of the diaphragm.

The plus 14 cm. of water pressure found in the right pneumothorax after death demands an explanation, since the maximum pressure ever reached in the peritoneal space during refills was only plus 8. It seems evident that the collapsible bleb on the pleural surface of the diaphragm acted as a valve while the diaphragm itself served as a pump forcing air through the valve. This pump-like action became more vigorous as increasing dyspnea caused greater respiratory effort. Thus a vicious cycle was established, the dyspnea produced by the partial collapse of the right lung increasing the action of the diaphragm which, in turn, pumped more air into the right pleural space creating further dyspnea.

It would seem that three main factors are pertinent in determining the seriousness of this complication of pneumoperitoneum: first, the size and suddenness of the rupture of the diaphragm; second, the volume and pressure of the pneumoperitoneum; and third, the valve effect that may occur which, associated with the pump-like action of the diaphragm, can set up a vicious cycle and result in a rapidly fatal course. These possibilities emphasize the need for careful observation of pneumoperitoneum cases since, if this complication occurs, early diagnosis and prompt treatment will be necessary to prevent a fatal outcome.

#### SUMMARY

A fatal case of rupture of the diaphragm and resulting tension pneumothorax in a patient receiving therapeutic pneumoperitoneum is reported. The autopsy findings and the pathological physiology involved are discussed along with factors that may determine the seriousness of this complication.

#### SUMARIO

##### *Neumotorax Hipertensivo Letal Debido a Rotura Diafragmatica en Paciente en Tratamiento con Neumoperitoneo*

El caso letal comunicado es de rotura del diafragma seguida de neumotorax hipertensivo en paciente que recibía el neumoperitoneo terapéutico. Al discutir los hallazgos autopsícos y la fisiología patológica, mencionanse los factores que pueden determinar la gravedad de la complicación.

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# TUBERCULOUS ARTERITIS OF THE ABDOMINAL AORTA WITH RUPTURE INTO THE THIRD PORTION OF THE DUODENUM

## Report of a Case

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### INTRODUCTION

Tuberculosis of the large arteries of the body has been of rare occurrence as evidenced by a review of the literature. The arteritis occurring in the small blood vessels is usually part of the tuberculous process that involves a particular organ and in itself is not very important, since it does not have any direct effect on the course of the disease. However, when the larger vessels are involved, a change in the immediate course of the disease ensues. In 1913, Haythorn (5) described four types of tuberculous arteritis. The first was milary tuberculosis of the intima which he stated was the most common. In this type, milary glistening tubercles were seen on the surface of the intima. The second consisted of polypi of tuberculous tissue attached to the intima. Here a small pear-shaped mass of tissue, which resembled a white thrombus, was attached by a pedicle to a slight elevation of the intima, with the distal portion swinging free in the direction of the blood current. The pathogenesis here consisted in deposits of tuberculous tissue on old sclerotic patches which were followed by thrombus formation over the area and which later became organized and assumed a polypoid mass. The third type was tuberculosis of the wall in which all the layers were involved, and the fourth type was aneurysm formation. According to Eppinger (4), aneurysms on a tuberculous basis are formed by mycotic emboli that enlodge in the vasa vasorum and cause a thrombosis which in turn results in an acute peri- and mes-arteritis with complete solution of the continuity of the elastica and damage to the adventitia with resulting aneurysm formation. However, aneurysms can also be formed by direct extension of a tuberculous process from within or from without.

The first case of a tuberculous aneurysm was reported by Kamen (6) in 1895. The patient was a soldier, 24 years of age, with chronic pulmonary tuberculosis and acute milary tuberculosis. The former caused an aneurysm of the ascending aorta just above the aortic cusps by direct extension from caseating mediastinal lymph nodes.

Until 1933, 20 cases were reported of aneurysms of medium size and large arteries as a result of tuberculosis. Four of these were due to hematogenous dissemination with bacilli going through the vasa vasorum and lodging in the medial wall. There were no foci of tuberculosis surrounding these arteries. The primary source of the tuberculosis was known in all cases. The first of these cases was reported by Pel and recorded by Lenoble (7) in 1922. It was that of a 20-year-old female who died of an aneurysm of a femoral artery and the superior mesenteric artery, both of tuberculous origin. There were also tubercles on the mitral valve. The second report was that of Tozer (11) in 1915 and described a case in which a tuberculous aneurysm of the abdominal aorta ruptured into the duodenum. The third was that of Brockman (3) in 1926 in the case of an aneurysm of a femoral artery in a boy 14 years of age who also had Pott's disease. Brockman believed that this aneurysm occurred as a result of a mycotic embolus to the vasa vasorum of the femoral artery. The fourth case was that of Malcolm (8) in 1928, in which a 72-year-old male had a femoral aneurysm which ruptured. Milary tuber-

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culosis was found in this patient and tubercle bacilli were demonstrated in the media. All the coats of the arterial wall were necrotic. In 1933, Baumgarten and Cantor (2), reported a case of a 53-year-old male with an aneurysm of a femoral artery which ruptured. This was treated surgically and the histological study proved it to be of tuberculous origin. The patient was well three years after the rupture occurred. In this case no primary focus was demonstrated. In 1935 Bernard (1) demonstrated a case of a 63-year-old female with tuberculosis of the coronary and intracranial carotid arteries. Here, too, no primary focus was demonstrated. Thieme and Maddock (10) in 1939 reported a case of a 35-year-old male with peripheral vascular tuberculosis. There was no primary focus ever demonstrated. In 1941, Neel (9) described a case of a 21-year-old pregnant female with tuberculous thrombophlebitis in the lungs and tuberculous involvement of an external iliac artery. The lumen of the artery was filled with a caseous white thrombus and there were areas of inflammation and caseous necrosis in the intima and media with proliferation of connective tissue and vascular endothelium and infiltration by lymphocytes and epithelioid cells in the adventitia. Tubercle bacilli were demonstrated in the white thrombus.

Thus, tuberculosis of the large arteries occurring as a result of hematogenous dissemination is indeed a rare occurrence. We are now presenting a case of tuberculous aortitis of the abdominal aorta without aneurysm formation which occurred through hematogenous dissemination and precipitated rupture into the duodenum with immediate death.

#### REPORT OF A CASE

A D., a 62-year-old white male was admitted to the Jewish Hospital because of continued fever, malaise, anorexia and weight loss of six weeks' duration.

His past history was significant in that twenty years before admission he had suffered a coronary artery thrombosis from which he apparently had recovered completely. At the age of 18 he had one bout of hemoptysis which subsided within one week and for which no therapy was given. He had retired from business and during the past twenty years had occasional angina and exertional dyspnea.

Six weeks before admission he had an episode of fever and malaise which lasted for a few days. He was treated with sulfadiazine. Following this episode he never fully recovered. He noted anorexia, fatigability, and weight loss. Two weeks before admission he had a recurrence of fever and malaise. This did not respond to therapy and necessitated hospital observation.

The physical examination showed a well nourished and well developed adult male. The blood pressure was 150 systolic, 100 diastolic (mm. of mercury), pulse 130 per minute, temperature 100° F., and respirations 26 per minute. All findings were negative except for (1) the heart was enlarged to the left by percussion and a soft apical systolic murmur was audible, (2) the liver was felt one and one-half finger breadths below the costal margin and (3) the spleen was felt one finger breadth below the costal margin.

Two days after admission the patient appeared slightly dyspneic and ex motie. Moist rales were audible at both bases and cleared slightly on coughing. A pericardial friction rub was heard in the second left intercostal space.

The urine showed a specific gravity of 1.022, albumin one plus, sugar zero, and 5 hyaline casts per high power field. The hemoglobin was 85 per cent, erythrocytes 4.10 million per cu. mm., total leukocytes 5.015 per cu. mm., with 85 polymorphonuclear leukocytes and 15 lymphocytes per 100 cells. The erythrocyte sedimentation rate varied from 9 to 12 mm. (Westergren).

The following studies were normal: blood sugar, urea, uric acid, total protein, A/G ratio, prothrombin time, serum agglutination for typhoid, paratyphoid group, Brucella, Heterophile antibody titer, serum malaise, cerebrospinal fluid, and four blood cultures.

The following studies were abnormal: a glucose tolerance test showed a normal curve with a mild glycosuria, and in electrocardiogram showed slight depression of S T segment in Lead I and the Q wave in Lead III, a circulation time study (arm to tongue) was twenty seconds, and a sternal puncture showed "smudge" cells.

A gastrointestinal roentgenographic study revealed an esophageal hiatus hernia and multiple diverticula in the descending and sigmoid colon. A chest roentgenogram revealed that the heart was enlarged to the left and that both lung fields contained numerous stippled deposits scattered from apex to base.

*Clinical course* The patient's temperature varied from 100 to 104°F for the first week and the pulse rate varied proportionately. The respirations, however, varied from 30 to 45 per minute. He was given procaine-penicillin and streptomycin. During the second week the temperature varied from 99° to 101°F. From the fifteenth to the eighteenth day it varied from 100° to 101°F, and the respirations were normal for the last eleven days of admission. The patient requested that he be discharged on November 17, 1948.

At home he continued to have low grade fever. He began to complain of aching pain in the lumbodorsal region and of lower abdominal cramp like pain. The week before the second admission his temperature rose to 104°F. On December 11, he was readmitted to the hospital.

A physical examination showed the patient to be in no distress but "toxic" and pale. A loud pericardial friction rub was heard at Erb's point. A pulmonic systolic murmur was also noted. The liver was enlarged three to four finger-breadths below the costal margin and had a firm edge. The spleen was firm and nontender. It was noted that the abdominal wall was easily palpable.

The following studies were normal: blood urea nitrogen, glucose, cholesterol, bilirubin, serum amylase, urine culture, urine and cephalin flocculation tests. The erythrocyte sedimentation rate was 25 mm per hour.

*Clinical course (final admission)* The temperature varied from 99° to 102°F and the pulse and respirations were proportional. On admission he complained of severe abdominal pain. At times he became irrational. On December 18, at 5:30 p.m. it was noted that the patient had a fair day. At 8:50 p.m. he suddenly began to have gasping respirations and died ten minutes later.

#### *Autopsy Findings*

*Lungs* The right lung weighed 600 Gm and the left 550 Gm. The external surfaces were smooth and glistening, but on palpation small hard nodules up to 0.3 cm. could be felt subpleurally and deep within the parenchyma. The cut sections revealed frothy fluid that could be expressed on pressure. All the lobes were similar. The pleural surface over the left apex was slightly dimpled and was covered by thin fibrous pleural thickening. The lung tissue subcent was firmer than the surrounding area. The bronchi were not unusual. The pulmonary arteries showed a mild degree of intimal sclerosis. The tracheobronchial lymph nodes were enlarged and soft. On cut sections they showed circumscribed areas of soft white and yellow tissue.

*Gastrointestinal tract* The stomach contained large clots of blood. The duodenum and jejunum were filled completely with a similar material. In a third portion of the duodenum there was a perforation through the posterior wall which communicated with the lumen of the abdominal aorta (figure 1). In the duodenum, lying freely, was a round mass of tan, red, and brown tissue measuring 4 cm. in diameter which fit snugly into the perforation (figures 2 and 3).

*Spleen* The spleen weighed 390 Gm. At one pole there was a yellow firm area which was depressed below the surface. The cut section showed this to be yellow and triangular in shape with its base at the surface of the spleen. The pulp was soft.

*Kidneys* The right kidney weighed 200 Gm and the left 220 Gm. The capsules stripped easily. The cortices were studded with small milium white nodules which on cut section contained soft white material.

*Lymph nodes* The lymph nodes in the area surrounding the aorta were not involved by a tuberculous process

*Pericardium* Both visceral and parietal pericardial layers were smooth and glistening and uninvolved by any pathologic process

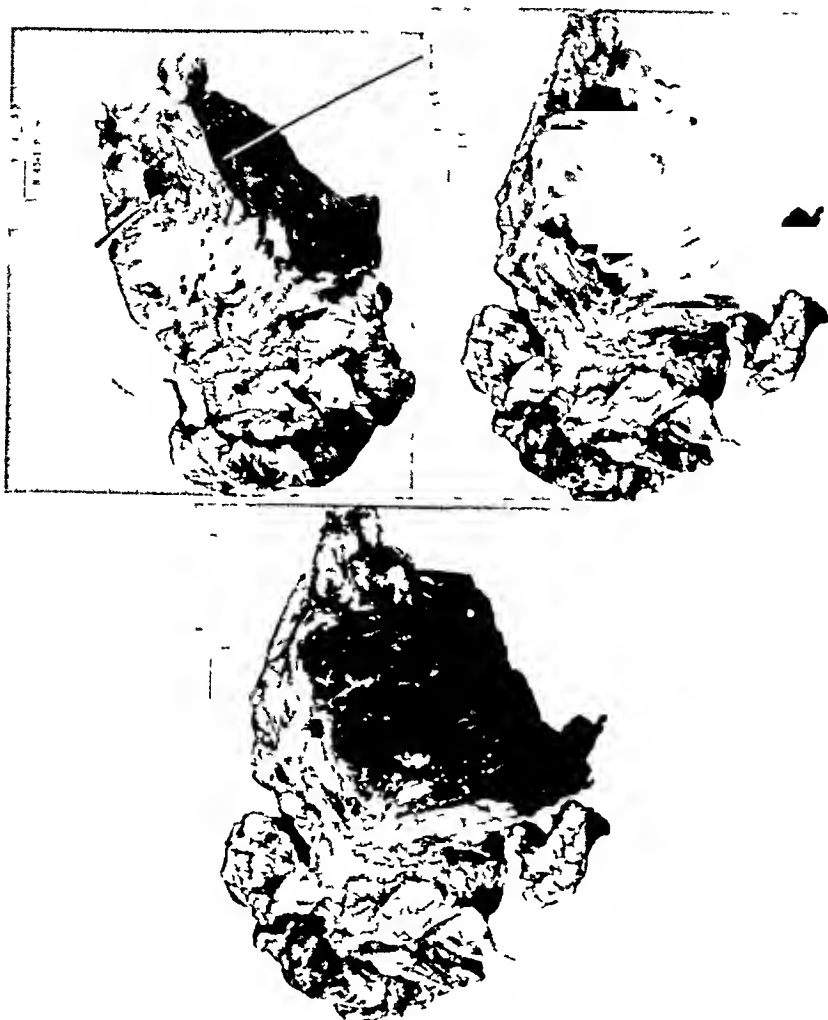


FIG. 1 (Upper left) Photograph showing probe passing from aortic lumen on the left into the darker duodenal lumen on the right

FIG. 2 (Upper right) Photograph of perforation from the duodenal side

FIG. 3 (Bottom) Photograph showing large clot occluding the perforation on the duodenal side

#### Microscopic

*Lung* In various parts within the interalveolar septa were found various sized tubercles consisting of caseating necrotic centers with Langhans' giant cells, epithelioid cells and lymphocytes at the periphery. Some of the tubercles were located subpleurally. Some of the alveoli contained a homogeneous pink staining material. In the apex of the left lung there was a small tubercle adjacent to an area of ossification and fibrosis.

*Liver* This showed small tubercles scattered throughout the lobules

*Adrenals* This showed one tubercle in the cortex and otherwise were not abnormal

*Prostate* This also showed one tubercle in the stroma and mild glandular overgrowth

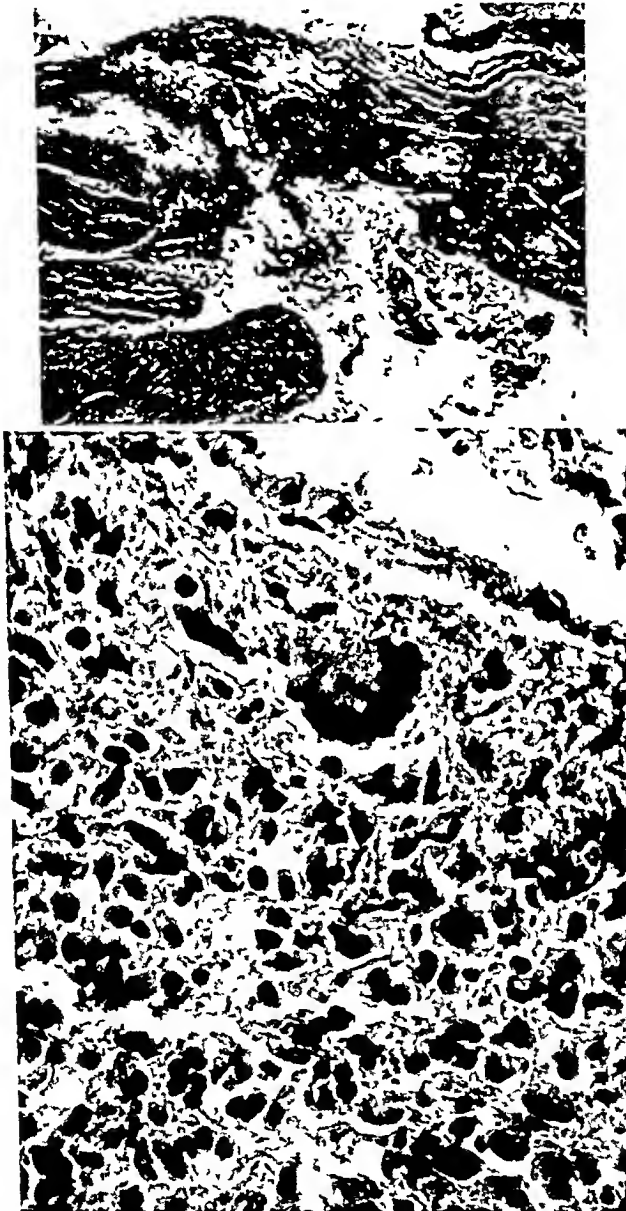


FIG 4 (Top) Microphotograph showing dissolution of continuity of aorta by caseation

FIG 5 (Bottom) Microphotograph showing tuberculous reaction in adventitia with a Langhans' giant cell, lymphocytes and epithelioid cells

*Kidney* The cortices were studded with various sized tubercles which were similar to those in the lung

*Spleen* This showed a large caseous infarct and many small tubercles within the parenchyma

*Aorta and site of perforation* The intima showed a large atheromatous plaque with many cholesterol clefts. The intima could be followed to a point where its continuity was interrupted by crusting, necrotic tissue. The continuity of the media and adventitia was also interrupted by similar material at the same point (figure 4). In these areas, especially in the adventitia, tuberculous granulation tissue consisting of Langhans' giant cells, epithelioid cells, lymphocytes, and fibrous tissue could be demonstrated (figure 5). A Ziehl-Neelsen histologic stain of these necrotic areas revealed the presence of a considerable number of acid-fast bacilli. There was no evidence of any aneurysm formation.

*Anatomic diagnosis (partial)* Tuberculosis, miliary, of lungs, liver, kidney, spleen, prostate, adrenal and tracheobronchial nodes.

Tuberculous aortitis of abdominal aorta with rupture into third portion of duodenum with hemorrhage.

Apical tuberculosis, old, left, with ossification.

#### COMMENT

It has been demonstrated that this case of tuberculous aortitis occurred through hematogenous dissemination, in as much as there were no tuberculous foci in the tissues surrounding this portion of the aorta and since it was directly associated with acute miliary tuberculosis. There are two possibilities as to how the invasion of the wall could have occurred. The first is that mycotic emboli entered through the vessel lumen and precipitated the aortitis. The second is that these same emboli could have implanted themselves upon an ulcerated atheroma of which there were many in this portion of the aorta. From here the invasion would be from within out. However, it is impossible to say which was the basic mechanism of invasion.

It is interesting to note that this is the only reported case in which aneurysm formation had not occurred.

The primary focus in all probability was the old tuberculous lesion found in the apex of the left lung, although no definite evidence of activity could be demonstrated.

This case further bears out the fact that tuberculosis of large arteries usually changes the immediate course of the disease.

#### SUMMARY

A case of tuberculous aortitis of the abdominal aorta with rupture into the duodenum is reported. The lesion was associated with generalized miliary tuberculosis which presumably arose from an old pulmonary tuberculous lesion. The aortitis was not associated with the formation of an aneurysm.

#### SUMARIO

##### *Arteritis Tuberculosa de la Aorta Abdominal, con Rotura en la Tercera Porcion del Duodeno*

La tuberculosis de las grandes arterias es rara.

Ofrecense un repaso de la literatura y un caso de arteritis tuberculosa de la aorta abdominal con rotura intraduodenal.

No hubo formacion de aneurisma.

Esta lesion se asocia granulosa, y se discute la patogenia.

Se da por sentado que el foco primario radica en una antigua lesion tuberculosa en el pulmon.

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*Addenda*

Since this paper was written, four other articles on tuberculous aneurysm of the abdominal aorta have come to the authors' attention

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## Letters to the Editors

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### THE CHEMOTHERAPEUTIC ACTION OF STREPTOMYCIN PARA-AMINOSALICYLATE IN EXPERIMENTAL TUBERCULOSIS IN MICE

*To the Editors of the American Review of Tuberculosis*

Lehmann in 1946 (*Lancet*, 1946, 1, 15) called attention for the first time to the tuberculostatic action of para-aminosalicylic acid *in vitro* and to its suppressive effect on the course of tuberculous infection in animals and man. Since then, many reports on the antituberculous activity of this substance have appeared (See Proc. Staff Meet. Mayo Clin., 1949, 24 (13), 342). Studies to date have emphasized (1) the large dosages of para-aminosalicylic acid necessary in order to influence the course of the infection when the oral route of administration is used, and (2) the frequent gastrointestinal disturbances resulting from the administration of these large doses.

In 1947, Youmans and his associates (*J. Bact.*, 1947, 54, 409) called attention to the possible synergistic effect of para-aminosalicylic acid on the action of streptomycin when the two tuberculostatic agents are used in combination. Preliminary clinical studies have been carried out since that time to study this synergistic action, and data are available to suggest that the administration of para-aminosalicylic acid in conjunction with streptomycin lowers the incidence of the emergence of streptomycin-resistant strains of tubercle bacilli (See Report of the Seventh Streptomycin Conference held by the U. S. Veterans Administration, Army, and Navy, April 1949). Large dosages of para-aminosalicylic acid (8 to 15 Gm. per day) have been used, however, throughout the studies.

The para-aminosalicylic acid salt of streptomycin is a highly purified compound consisting of 56 parts of streptomycin and 44 parts of para-aminosalicylic acid. One molecule of pure streptomycin base combines with 3 molecules of para-aminosalicylic acid (1-aminosalicylic acid) to form the water-soluble salt, streptomycin para-aminosalicylate. It has a molecular weight of 1,039 and a theoretical potency of 55.8% of pure streptomycin base per mg. total weight of salt. Preliminary studies of the tuberculostatic activity of this salt (Hobby *et al.*, Report of the Seventh Streptomycin Conference held by the U. S. Veterans Administration, Army, and Navy, April 1949) have indicated that it is approximately twice as active *in vitro* as streptomycin alone when compared on a streptomycin unitage basis. Streptomycin-resistant mutants of *M. tuberculosis* may or may not be sensitive to this salt, all the more sensitive to it, however, than to streptomycin sulfate (see table 1).

*In vitro* studies to demonstrate the emergence of strains resistant to streptomycin para-aminosalicylate have failed to show such mutants during a three months' study. It is recognized that this does not mean that such resistant organisms will not appear under appropriate conditions. The data available suggest, however, that the incidence with which strains resistant to this salt will appear is low.

Streptomycin para-aminosalicylate may be administered without difficulty to animals and man. This salt permits the administration of streptomycin and para-aminosalicylic acid simultaneously in a single injection. Its activity *in vivo* is therefore, of interest.

A study of the chemotherapeutic action of streptomycin para-aminosalicylate in

comparison to that of streptomycin sulfate was carried out in mice infected intracerebrally with the H37Rv strain of *M. tuberculosis*. The results of this study indicate that the para-aminosalicylic acid salt of streptomycin, in dosages equivalent to 400  $\gamma$  of pure streptomycin base, is more effective than the same quantity of streptomycin sulfate. This effect may be evidenced by comparison of both the average survival time and the actual per cent survival at the end of the observation period (see table 2).

TABLE 1  
*The In Vitro Tuberculostatic Activity of Streptomycin Para-aminosalicylate*

CULTURE	SENSITIVITY ( $\gamma$ PURE STREPTOMYCIN BASE PER CC.)	
	Streptomycin Sulfate	Streptomycin PAS
H37Rv	0.5	0.23
Variants (H37Rv)		
7 strains	>10,000	1,163-2,325
1 strain	6,000	930
1 strain	1,250	<9.3
Freshly Isolated		
3 strains	<1	0.23-0.50
2 strains	2-10	0.90-8.0
1 strain	25	7.4
2 strains	>100	<1.9-29.3
1 strain	5,000	10.0

Sensitivity = least amount necessary to inhibit growth at the end of 12 days' incubation in Dubos liquid medium.

TABLE 2  
*The Chemotherapeutic Activity of Streptomycin Para-aminosalicylate in Experimental Tuberculosis in Mice*  
(Strain H37Rv)

THERAPY		PER CENT SURVIVAL/MONTHS				AVERAGE SURVIVAL TIME/DAYS CALCULATED AT (MONTHS)			
Agent	Dosage SM $\gamma$ /day	1	2	3	4	1	2	3	4
SM-PAS	400	100	100	90	90	30	60	89	114
SM-SO <sub>4</sub>	400	60	50	40	40	28	43	57	72
Controls	—	70	30	30	10	29	41	50	61

All animals in this experiment were treated for one month only. The number of animals used was small (10 per dosage). Repeated experiments on large numbers of animals, however, have shown comparable results.

The para-aminosalicylic acid salt of streptomycin is nonirritating in animals upon repeated injection at the same site. It possesses the same degree of acute toxicity for lower animals as does the calcium chloride double salt of streptomycin. Chronic toxicity studies in cats indicate that the toxicity of the PAS salt of either streptomycin or dihydrostreptomycin should be the same in man as that of streptomycin or dihydrostreptomycin, respectively.



By injection the small amount of para-aminosalicylic acid present in this compound appears to be sufficient to alter the course of tuberculous infection in mice. The true value of this salt, however, will depend upon whether or not the amount of para-aminosalicylic acid present is sufficient to alter the incidence of emergence of streptomycin-resistant strains of *M. tuberculosis* in man. This can be determined by clinical trial only, and studies are in progress to determine the rate of absorption of streptomycin para-aminosalicylate, its therapeutic value, toxicity, and ability to prevent the emergence of streptomycin-resistant organisms in tuberculous individuals.

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October 13, 1949

## THE EFFECT OF ANTIHISTAMINE MEDICATION ON THE TUBERCULIN REACTION

*To the Editors of the American Review of Tuberculosis*

I have read with considerable interest the article in the September 1949 number of the *American Review of Tuberculosis* by Doctors Friedman and Silverman on "The Effect of Antihistamine Medication on the Tuberculin Reaction in Children." In the light of my own experiences with antihistamine drugs, I am certain that the results of their study are rendered delusive by several factors: first, by inferring at the outset the relationship of the skin reaction to histamine and other allergens, such as ragweed, and timothy, to the skin reaction in an individual hypersensitive to tuberculin, second, by expecting to see results with "homeopathic" doses of antihistamine used for only four days (even the ten children given large doses received the drug for only two days prior to the skin test and for two days thereafter), third, the tests were run on children from five to eleven years old. In children of this age group the degree of hypersensitivity is less than that seen in young adults and older humans.

In a series of cases of various types of tuberculosis in which antihistamines were employed to study both the effects on the Mantoux test and the tuberculous lesions, reported in *Annals of Allergy*, May-June 1949, 7, 306, we found some very interesting results when adequate dosage and time were also employed. When 500 milligrams of drug were given for six months with pulmonary and other forms of tuberculosis, one begins to see the results that cannot possibly be seen by employing 60 milligrams for four days. In 24 of the 30 cases reported, the Mantoux (using PPD, first strength) was converted gradually to negative and remained negative, except for a few instances, for the duration of the antihistamine therapy. All skin tests returned positive within four weeks after medication was discontinued. Some very interesting effects on pulmonary lesions, some quite dramatic, are also demonstrated.

However, it is quite unfair to correlate visceral (pulmonary) hypersensitivity with the state of the skin reaction and, therefore, the degree of visceral response cannot be correlated with the degree of skin response to antihistamines. This is apparently true in all forms of allergy. Actually, the skin test with any allergen is a pretty poor index of hypersensitivity elsewhere. This is one important failure in the usual skin tests for allergies.

I cannot agree that, as the authors state, the therapeutic effectiveness of the various antihistamines are quite similar. Anyone with hay fever will quickly disagree with that statement, but also we found in our intensive studies that a change to one other antihistamine in the group of drugs employed would sometimes bring about a change in the Mantoux or lesion which the other antihistamine was, to all appearances, incapable of producing in that particular patient. Patients with allergies are often benefited by one and not by another of the antihistamines and, as well, will become refractive to one drug after a time, and not to another.

I sincerely hope that this criticism will tend to make those who plan to use antihistamines and other drugs experimentally more aware of the importance of adequate time and dosage in the proper evaluation of the results. Bacterial allergy is probably an important factor in all infections, and experimentation along these lines is now being carried on in a number of laboratories and institutions. It is extremely important now that a plea be made for very careful evaluation of methods used and results obtained. This especially applies to time and dosage.

ALFRED R. HENDERSON

MINNAPUS TRANSSEFF  
OCTOBER 3, 1949



BRUCE W DOUGLAS  
1892-1949

## Bruce W. Douglas

1892-1949

Bruce Douglas lost his life in an automobile accident August 11, 1949. Quiet, kindly, thoughtful, wise, humble Bruce Douglas! His death leaves a large void in three areas of activity—in tuberculosis and public health within his chosen profession, and in religion—for in each of these he established himself as a leader and counsellor of first water.

Doctor Douglas was born in Des Moines, Iowa, on August 26, 1892, the son of John Henry, Jr., and Mabel Hutchinson Douglas. In 1915 he was graduated from Whittier College, California, where he was a member of the baseball team. Following then in order were his M.D. degree from Rush Medical College of the University of Chicago, internship at Harper Hospital, Detroit, and assistant residency at Herman Kiefer Hospital where he began a career in tuberculosis work in which he became prominent. Shortly after he transferred from Kiefer to the Maybury Sanatorium (also operated by the Detroit Department of Health) his capacities brought him to the superintendency of the latter institution. He had held this position for ten years when he relinquished it to become Controller of Tuberculosis of that city. His eight years as Controller set many examples for the country, for the Detroit campaign against tuberculosis was exceptionally active and fruitful. From this position it seemed but a natural and logical move that he should succeed to that of Commissioner of Health of that city upon Doctor Henry Vaughan's resignation. At the time of his tragic death he ranked among the leading health officers of the nation.

As president of the American Trudeau Society in the year, in Boston, when the new constitution was adopted, he evoked the admiration of all by the remarkable manner in which the day-long session was conducted. All were impressed with what adroitness and eminent fairness the chairman of the day presided over the discussions, many of them featured by feeling and heat. Few knew that he had anticipated the need of complete familiarity with parliamentary usage and characteristically had perfected himself in it beforehand.

From 1939 to the time of his death, Doctor Douglas served as a member of the Board of Directors of the National Tuberculosis Association, doing faithful work on numerous committees the while. He was a member of the Executive Committee in 1939 and 1940, and the Association elected him president for the year 1941-1942. Doctor Douglas was a member of the Editorial Board of the American Review of Tuberculosis from 1938 to 1947.

From 1941 he served as Professor of Preventive Medicine and Public Health in the School of Medicine, Wayne University, and as Lecturer on Public Health in the School of Public Health of the University of Michigan. He was a certified specialist in the American Board of Internal Medicine, a fellow in the American College of Physicians, American Association for the Advancement of Science, American Public Health Association, and American Medical Association. He held membership in numerous other national and local associations and was on

the governing boards of several medical, philanthropic, and social organizations of both national and local scope. During World War I he was a private and in the last war was Surgeon, United States Public Health Service Reserve Corps.

His scientific contributions to our expanding knowledge of tuberculosis and public health have been marked for their quality and range.

Born into the Society of Friends, this "quiet Quaker" lived and exemplified a fine philosophy of life. He was interested in human behavior and was wise. His counsel was often sought. Whether the appeal came from the American Friends Service Committee, the Interracial Commission of Detroit, a staff of physicians with a problem from the sickroom, an auditor from the Budget Bureau, or an innate citizen with a grievance, his reaction and advice always seemed to be born of wisdom and understanding.

Always soft spoken, unaffected by his success, and approachable if sometimes almost shy, he was friend to everyone. He was capable of prodigious effort and work yet never appeared to be hurried, for there was always abundant time for any who wanted to see him. His daily life was the embodiment of unselfishness, and perhaps his most outstanding personal trait was humility. In the days of the depression and later of the war, he spent endless hours over adjustments, and, with steadfast devotion, was attentive to the unmet needs of patients and employes. His trials he met with remarkable serenity and rare wisdom. He achieved eminence but maintained humility. He was a good man—good without smugness—and, I think, the best and kindest man I have known.

Bruce Douglas is dead. The depressing significance of the fact bears down upon those who knew and loved him and those who depended upon him for advice, help, and interest. But his life was an extraordinarily useful one. He leaves his family a splendid heritage, and all, a worthy example.

H S WILLIS

## BOOKS

H. McLEOD RIGGINS AND H. CORWIN HINSHAW (Editors) *Streptomycin and Dihydrostreptomycin in Tuberculosis* Pp. xiii-554, National Tuberculosis Association, New York, N. Y., 1949, cloth, \$7.50

This volume of 554 pages is composed of 33 papers on various aspects of streptomycin and tuberculosis grouped for convenience under eight major headings, including historical aspects of the subject, the relation of the American Trudeau Society to early studies, bacteriological and pathological aspects of the problem, detailed and summarizing reports on the clinical experience of Trudeau Society investigators, experimental and clinical studies on dihydrostreptomycin, and, finally, investigations of combined therapy, with emphasis on the adjuvant effect of para-aminosalicylic acid in treatment. Sixteen, or approximately one-half of the papers, are reprints of previous publications. These include three of the original classics on the subject, viz., the paper by Schatz and Waksman giving the first detailed report on the effect of streptomycin on the tubercle bacillus, and the two well-known papers by Feldman and Hinshaw describing the first tests of the value of streptomycin in the treatment of tuberculosis in experimental animals and man. The other seventeen papers represent original contributions, the majority of which are an outgrowth of a carefully planned therapeutic trial program on the clinical value of streptomycin organized in 1946 by a group of clinical and laboratory investigators in the Trudeau Society.

The volume was planned originally as a report to the six streptomycin producers who made the study possible by contributing enough streptomycin, at a time when the drug was very costly, for the treatment of 1,000 tuberculous patients. During the course of preparation of this report such great development of the subject occurred that it appeared highly advantageous, in the interest of a broad understanding of the value of streptomycin in the treatment of tuberculosis, to supplement the individual and summarizing reports by members of the Trudeau Society group with papers resulting from other important research, much of which, like the studies of the Tuberculosis Study Section of the Research Grants Division of the National Institute of Health, was stimulated by the Trudeau Society investigation. The volume includes reports of work sponsored by these two groups, a summary of results of a very extensive cooperative streptomycin program of the Veterans Administration, U. S. Army, and U. S. Navy, and two papers sponsored in part by the Committee on Chemotherapeutics and Other Agents of the National Research Council. It is interesting to note that certain of the investigators submitting reports in this volume were actively concerned in the programs of all of these organizations. Thus the volume as a whole represents a remarkable combination of experience.

The bacteriological and pathological papers present fundamental data fur-

nishing a convenient source of information on a multitude of problems in these fields. Included are accounts of the sensitivity and resistance of tubercle bacilli to streptomycin and the histological character of the effect of streptomycin on tuberculous lesions in animals and man. In this section is a fine paper also by Feldman on critical evaluation of a chemotherapeutic agent through animal experimentation.

The chief interest of the general reader will be focused on the Summary Report of the Streptomycin-Tuberculosis Research Project of the Trudeau Society. In the analysis of clinical data from the cooperative enterprise, the editors had the able assistance of Dr. Carroll E. Palmer and Mrs. Shirley H. Ferebee, of the Field Studies Section, Tuberculosis Division, Public Health Service. A series of charts in this section, which deal specifically with the value of different regimens of streptomycin, indicate that streptomycin is of greatest efficacy in acute forms of tuberculosis, that large daily doses, although more toxic, are definitely more effective than small doses, that the development of drug-fastness of infecting tubercle bacilli is directly related to the length of treatment, and that relapse of the disease after treatment increases with the passage of time, a fact emphasizing the necessity of supplementing streptomycin treatment with other therapeutic measures of established value.

The six papers on dihydrostreptomycin included in the volume are reprints of the well-known series which appeared in the *American Review of Tuberculosis* in November 1948. More than any others these papers point up the difficulty of keeping abreast of developments in a rapidly expanding field through the medium of monographs like this one. The current principal questions on the place of dihydrostreptomycin remain unanswered, because they arose too recently for inclusion.

The final section is in the field of apparent greatest promise, combined therapy. The volume closes on a note of optimism cautiously expressed, on the effect of para-aminosalicylic acid in delaying the emergence of streptomycin-resistant strains of tubercle bacilli.

The volume will be of great value to practicing clinicians and investigators alike. Although loosely organized, as a result of change in its objective in the actual course of its preparation, it loses little of its usefulness thereby, for its chief and lasting value will be as a reference source book in the many fields covered. It is reasonable to expect that its value for the therapeutic results described and the expert analyses based upon them will be ephemeral, for the results of much larger studies, well supported by critical analysis, may be expected in the near future. The volume is timely at present, however, and furnishes a remarkable picture of cooperation in clinical investigation. The summaries and analyses of results of investigation inter-spersed throughout the book illustrate clearly the value and also the limitations of the extraordinary drug on which the book is based. Great credit is due the editors and publishers in making such a compilation possible.

EDMOND R. LONG

LARS WERKOE *The Influence of Positive Pressure Breathing on the Circulation in Man, Acta medica Scandinavica, Stockholm, Sweden, 1947*

This is a short monograph describing the effects on the circulation of various forms of positive pressure breathing, specifically, artificial respiration by intermittent (inspiratory) positive pressure, spontaneous respiration under continuous positive pressure, and spontaneous respiration against expiratory positive pressure. Most of the work was concerned with inspiratory positive pressure breathing (IPB), several artificial respirators designed by the U S Army Air Forces were used. The research was done by the author at Bellevue Hospital, New York City, in collaboration with Cournand and associates.

After a review of the literature, a detailed description is given of the methods employed in the author's work, including the technique of right heart catheterization, the determination of cardiac output, and the recording and analysis of peripheral arterial and of right heart and pulmonary arterial pressures.

The subjects studied consisted of fourteen individuals with normal circulation and twelve with various forms of cardiovascular disease, some compensated, others in failure. In the subjects with normal circulation, intermittent positive pressure breathing caused increased arterial blood pressure and increased mean and diastolic pressures in the right ventricle and pulmonary artery, proportional to the applied mean mask pressure, but usually less than the applied pressure. When the mean mask pressure exceeded plus 5 mm of mercury, the cardiac output decreased significantly, and in proportion to the height of the mean mask pressure. Mean mask pressures in the region of plus 12 mm of mercury caused decrease in cardiac output of about 30 per cent. Total peripheral resistance increased with increasing mask pressure in the systemic circuit, and usually in the pulmonary circuit.

Further analysis of these results was made in three subjects in whom pleural pressures were recorded in addition to the other measurements. During the positive pressure inspiratory phase, right auricular and right ventricular diastolic pressures increased, but less than the increase in pleural pressure. Right heart filling was thus decreased, which was interpreted as indicating that right heart output was also decreased. Left ventricular output, on the other hand, was considered to be increased during positive pressure inspiration, due to the forcing of additional blood from lungs into the left heart. During expiration, net filling pressure in the right heart (diastolic right ventricular pressure minus pleural pressure) was increased, indicating increased cardiac output. Evidence for this interpretation was provided by the facts that the average net filling pressure in the right ventricle for the whole respiratory cycle was found to change proportionally to the changes in cardiac output, and that the greater the number of beats during the respiratory cycle, that occurred with low filling pressures, the greater the decrease in cardiac output. The suggestion was made that, when intermittent positive pressure breathing is used for artificial respiration, the inspiratory period should be short and the expiratory period long, to avoid decreasing the cardiac output.



In one patient with heart failure, positive pressure breathing, producing decreased filling pressure in the right ventricle, resulted in an increased cardiac output

A finding of special interest, outside the pressure breathing studies, was that in normal subjects breathing 10 per cent oxygen at normal or atmospheric pressure there occurred a definite rise in pulmonary artery pressures

Expiratory positive pressure breathing caused only small changes in blood pressures and cardiac output. In one case, continuous positive pressure breathing with a low mean mask pressure resulted in a reduced cardiac output and increase in arterial right ventricular and pulmonary artery pressures

DICKINSON W. RICHARDS, JR

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